Naloxone HCl Prolonged Release Tablets

Advisory Committee

Information Book

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Advisory Committee Briefing Materials:

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INSTRUCTIONS TO THE COMMITTEE MEMBERS

This document consists of an Executive Overview followed by more detailed summaries to support the Executive Overview. The Executive Overview was designed to provide an **interpretive summary** of the information Develco considers key to understanding its development program and its positions about the program and current results. By reading it first, the committee member with time constraints can get a clear idea of the company's position and what it considers the key concerns to interpreting it.

Furthermore, the Overview is hyperlinked and cross referenced so that the reader who wants more information on a specific topic or concern can easily navigate to that part of the document for an in depth discussion. The Overview is not part of the document's overall numbering scheme.

For those reviewing this document in electronic format, individual topics are hyperlinked to the corresponding sections. For those reviewing this document in paper format, the specific section numbers are provided.

Each of the major sections in the following document provides a more in depth discussion of a particular area. Even though the discussion is in depth, the amount of raw data is limited because of the volume potentially available and because of the limitations for many committee members. The document provides references and appendices containing raw data, topics deemed secondarily connected to the issues at hand, and key literature sources.

This structure allows readers to get a picture of the company's position and to read in response to this position. It allows people to turn directly to their areas of expertise and allows readers to turn directly to data for analysis.

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LIST OF ABBREVIATIONS

AADPAC	Anesthetic and Analgesic Drug Products Advisory Committee
ADR	Adverse Drug Reaction
AE	Adverse Event
AUC	Area under the plasma concentration-time curve
BfArM	Bundesinstitut für Arzneimittel und Medizinprodukte (Federal Institute for Drugs and Medical Devices), Germany
BFI	Bowel function index
BID	Twice daily
BM	Bowel movement
BSFS	Bristol stool form scale
CI	Confidence interval
C_{max}	Maximum plasma concentration
CNS	Central nervous system
CSBM	Complete spontaneous bowel movement
CV	Cardiovascular
DDD	Defined daily dose
DGIEP	Division of Gastroenterology and Inborn Errors Products
ECG	Electrocardiogram
ENS	Enteric nervous system
EU	European Union
FDC	Fixed-dose combination
GCP	Good clinical practice
GI	Gastrointestinal
GKV	Gesetzliche Krankenversicherung (German statutory health insurance system)
HyMo	Hydromorphone
IC_{50}	Half maximal inhibitory concentration
ICSR	Individual case safety report
ID	Identification
i.m.	Intramuscular administration
IND	Investigational New Drug
IPC	Ischemic preconditioning
i.v.	Intravenous administration
K_i	Inhibition constant
LC-MS/MS	Liquid chromatography – tandem mass spectrometry
LD_{50}	Median lethal dose
LLOQ	Lower limit of quantification

MAA	Marketing authorization application
MACE	Major adverse cardiovascular effects
MDD	Maximum daily dose
MHRA	Medicines and Healthcare products Regulatory Agency, UK
MTD	Maximum tolerated dose
NDA	New Drug Application
NLX	Naloxone
NOAEL	No observed adverse effect level
OBD	Opioid-induced bowel dysfunction
OIC	Opioid-induced constipation
Oxy	Oxycodone
PAC-QOL	Patient Assessment of Constipation – Quality of Life
PAC-SYM	Patient Assessment of Constipation - Symptoms
PK	Pharmacokinetic
PR	Prolonged release
PRR	Proportional reporting ratio
PT	(MedDRA) preferred term
PV	Pharmacovigilance
QD	Once daily
SAE	Serious adverse event
SBM	Spontaneous bowel movement
s.c.	Sub-cutaneous administration
SDR	Signal of disproportionate reporting
SMQ	Standardized MedDRA query
SOC	System Organ Class
SOWS	Subjective Opioid Withdrawal Scale
$t_{1/2}$	Plasma concentration half-life
TDD	Total Daily Dose
t_{max}	Time to maximum plasma concentration
US	United States of America
WHO	World Health Organization
X^2	Chi-squared distribution

EXECUTIVE OVERVIEW

Develco Pharma Schweiz AG (Develco) is developing Naloxone HCl Prolonged Release Tablets (NLX PR Tablets), a prolonged-release (PR) oral tablet formulation of naloxone that will be available in multiple strengths from 3 - 48 mg. NLX PR Tablets are intended to be used freely with any opioid for the treatment of opioid-induced constipation (OIC). Since this is a mono-preparation instead of a fixed-dose combination (FDC) product, the dose of naloxone can be titrated to an individually safe and effective level for each patient (Sections 2.1, 2.5, and 4.2). Upon approval, NLX PR Tablets will be the first oral naloxone mono-preparation approved in the US.

Develco has completed two single-dose pharmacokinetic (PK) studies and is currently conducting two safety and efficacy trials in the European Union (EU) to support a European Marketing Authorization Application (MAA). Develco has also conducted a Pre-IND meeting with the FDA Division of Gastroenterology and Inborn Errors Products (DGIEP) and is in ongoing discussions about the clinical program required for a US New Drug Application (NDA) (Section 2.2).

The FDA has scheduled a meeting of the Anesthetic and Analgesic Drug Products Advisory Committee (AADPAC) to discuss the safety requirements for new drug applications (NDAs) for μ-opioid receptor antagonists to treat OIC in light of potential serious cardiovascular (CV) effects. As part of this meeting, the FDA has invited Develco to present data on its opioid antagonist product to inform the committee of the following topics: gut selectivity of NLX PR Tablets, potential to produce withdrawal, potential link between opioid withdrawal and CV effects, and other potential links between NLX PR Tablets and cardiovascular effects.

In this information book, Develco will describe the publicly-available data indicating that orally administered prolonged-release naloxone is highly localized in and selective to the gut. Due to its negligible systemic bioavailability and low peak plasma concentrations, orally administered prolonged-release naloxone is highly unlikely to induce systemic effects, including major adverse cardiovascular events (MACE) and withdrawal (Section 3.1.2). Develco will also present data from its own clinical investigations corroborating the low systemic bioavailability and low maximum plasma concentrations of naloxone (Section 2.4). Finally, Develco will present pharmacovigilance (PV) data from the extensive use of oral prolonged-release naloxone formulations in Europe that reveal no evidence of a cardiac safety signal or association between withdrawal and cardiac events (Section 4.3). In summary, the data from Develco's own program, along with data from decades of use in Europe, do not suggest an increased risk of cardiac events or MACE that are associated with opioid withdrawal. The potential for withdrawal, MACE, or other CV adverse events will be carefully monitored in the US phase 3 program and in post-marketing evaluation.

Naloxone is a well-known and extensively used opioid receptor antagonist that has no agonistic or morphine-like properties characteristic of other opioid receptor antagonists. Naloxone acts by competitively binding to opioid receptors, binding most strongly to the μ-

opioid receptor but also showing antagonistic activity at the κ- and δ-opioid receptors. Parenterally administered naloxone has been used acutely for reversal of opioid overdose for decades in the US and globally (Section 3). When taken orally, naloxone has been shown to reverse the effects of OIC, most likely by antagonizing μ-opioid receptors locally in the gut.

Unlike parenterally administered naloxone, oral prolonged-release naloxone has very low systemic bioavailability. High first-pass metabolism in the gut and liver results in low levels of systemic concentrations of the parent compound naloxone (Sections 2.4 and 3.1.2). The major metabolite, naloxone-3-glucuronide, formed through intestinal and hepatic first-pass metabolism, shows negligible binding at μ-, κ-, and δ-opioid receptors and can be considered inactive (Sections 2.3 and 3.1.2.3). Therefore, orally administered naloxone in the NLX PR Tablet formulation is selective to the gut, alleviating OIC by acting locally, not peripherally, on μ-opioid receptors in the gastro-intestinal (GI) tract. Because naloxone is not present systemically at significant concentrations, orally administered prolonged-release formulations of naloxone are highly unlikely to induce systemic effects, including CV effects or withdrawal (Sections 3.1.2)

A large population of patients has been treated with naloxone-containing oral FDC products in both the US and the EU. FDC products containing naloxone with an opioid agonist are marketed in the US since 1982 (Talwin®Nx and its generic versions, pentazocine/naloxone; Maximum Daily Dose [MDD] of naloxone: 6 mg) and in Germany since 1978 (Valoron® N, tilidine/naloxone; naloxone MDD: 48 mg) for the treatment of pain. Additionally, sublingual Suboxone® (buprenorphine/ naloxone; naloxone MDD: 4 mg) is approved in the US for the treatment of opioid dependence. The naloxone component in these combination products is intended to reduce the potential for diversion and abuse. Targin®/Targinact®, an oral FDC product containing prolonged-release oxycodone and naloxone at a 2:1 ratio (naloxone MDD: 40 mg), was approved in 2006 in the EU for the treatment of severe pain. The naloxone component in Targin®/Targinact® is specifically intended to reduce OIC, unlike in previous oral naloxone-containing products (Section 3).

GUT SELECTIVITY

Single- and multiple-dose pharmacokinetics (PK) studies with oral naloxone FDC formulations including Valoron® N retard (prolonged-release tilidine + naloxone) and Targin® (prolonged-release oxycodone + naloxone) show that only approximately 2-3% of the administered naloxone reaches systemic circulation. The major metabolite is naloxone-3-glucuronide, which is present systemically but shows no activity at opioid receptors based on receptor affinity studies. Develco's own single-dose PK studies confirm low systemic bioavailability of naloxone. These PK data suggest that oral prolonged-release naloxone acts locally at μ-opioid receptors in the gut but can be predicted to have no appreciable systemic effects.

Pharmacokinetic Studies using Oral Naloxone

Previously published studies with orally administered naloxone formulations have shown that it is rapidly and readily absorbed from the GI tract (~75% absorption). However, naloxone undergoes extensive first-pass metabolism and is rapidly and almost completely inactivated following absorption (Section 3.1.2.1 and 3.1.2.3), with naloxone-3-glucuronide as the major metabolite.

The absolute bioavailability of prolonged-release naloxone from oral doses of 5 mg to 120 mg was recently evaluated in healthy subjects. The absolute bioavailability ranged from 0.9% - 2%, which is in good agreement with earlier reports of approximately 2-3% bioavailability. A separate study using a very high oral dose of 500 mg immediate-release naloxone in healthy volunteers confirmed the drug's rapid absorption and considerable first-pass metabolism. The plasma concentration of the main inactive metabolite naloxone-3-glucuronide was approximately 700-times higher than that of naloxone (Section 3.1.2.1).

It should be noted that in studies with Targin® (prolonged-release oxycodone/naloxone), systemic naloxone levels were substantially increased in patients with renal or hepatic impairment (Section 3.1.2.5). Develco has discussed these data with the FDA and plans to address the use of NLX PR Tablets in these special populations prior to an NDA.

Pharmacokinetic Studies using NLX PR Tablets

Develco has conducted two single-dose PK studies in healthy subjects with NLX PR Tablets: a dose proportionality study (Study 389B12), and a food effect study with the 48 mg strength that included an additional arm to characterize the prolonged-release properties of the formulation vs. an immediate-release oral solution (Study 444B12). Additional PK studies, including steady-state studies, are planned but have not been completed at this time. This first stage of the PK program has been conducted under good clinical practices (GCP) and is considered adequate to support an EU MAA. The second stage of the PK program to support US approval is under discussion with the FDA and will be completed prior to NDA submission.

The data from Develco's single-dose PK studies confirm that orally administered prolonged-release naloxone undergoes high first-pass metabolism and is present at low levels in the plasma. In the dose proportionality study (Study 389B12) the mean peak naloxone-3-glucuronide plasma concentration (C_{max}) was ~600 fold higher and the total naloxone-3-glucuronide exposure (AUC) was ~475 fold higher than for naloxone after dosing with the 48 mg strength of NLX PR Tablets (Section 2.4.1). These findings were replicated in the food effect study (Study 444B12). Compared to an immediate-release oral solution of naloxone, NLX 48 mg PR Tablets resulted in 4-fold lower peak plasma concentrations (C_{max}) and 24% lower total exposure (AUC) of naloxone. Of note, there was no statistically significant difference between subjects fasted or fed (Section 2.4.2).

Receptor Affinity Study

To address concerns that the major metabolite naloxone-3-glucuronide is systemically active and might result in withdrawal symptoms, reduced pain management, or have direct activity on cardiac opioid receptors, Develco has conducted a receptor binding affinity study with naloxone and naloxone-3-glucuronide to determine the relative binding potential to μ-, δ-, and κ-opioid receptors (Section 2.3). The binding affinity of naloxone on the three opioid receptor subtypes falls within the range of other μ-opioid receptor antagonists being investigated for the treatment of OIC. However, the results of the study confirm that naloxone-3-glucuronide shows essentially no affinity to the δ- and κ-receptors, and has dramatically less affinity to the μ-opioid receptor (more than 50,000-fold lower than the parent compound). These results are consistent with the conclusion that naloxone-3-glucuronide is an inactive metabolite (Section 2.3).

POTENTIAL FOR WITHDRAWAL AND MAJOR ADVERSE CARDIOVASCULAR EVENTS

The potential for μ-opioid receptor antagonists to induce MACE either directly or via withdrawal is discussed in section 4.1. Although naloxone has similar ability to bind μ-, κ-, and δ-opioid receptors as other μ-opioid receptor antagonists, the risk of naloxone causing withdrawal and precipitating MACE depends on the active substance being absorbed and present in the systemic circulation. With orally administered NLX PR formulations, the risk of withdrawal is low because there is little systemic naloxone available to cross the blood brain barrier. Likewise, there are insufficient naloxone concentrations to act peripherally on δ- and κ-opioid receptors in the heart or vasculature. Develco's own studies show that very little naloxone is available in the plasma after single-dose administration (Section 2.4). In particular, the IC_{50}/C_{max} ratios for all three opioid receptor subtypes, reflecting the therapeutic index of naloxone when administered orally as a prolonged-release formulation, are in a range making it highly unlikely that - even at the highest dose - plasma concentrations could reach a level required to exert any antagonistic effect (Section 4.2.4).

Potential for Withdrawal Effects

Naloxone has been marketed for decades in the US under various trade names (e.g., Narcan®) as a solution for intravenous (i.v.), intramuscular (i.m.), or subcutaneous (s.c.) injection for complete or partial reversal of opioid-associated respiratory depression. In subjects dependent on opioids, it is known that systemic naloxone can induce moderate-to-severe withdrawal syndromes very similar to that seen after abrupt withdrawal of opioids (Section 3).

Several early small-scale studies investigating oral immediate-release naloxone solutions for the treatment of OIC have found evidence of withdrawal in some patients. These studies used immediate-release naloxone solutions at varying concentrations and varying ratios of

naloxone-to-opioid dose. In most cases, these studies reported that the withdrawal symptoms were quickly reversed by opioid rescue medication (Section 3.1.3).

Larger studies were conducted for the EU approval of Targin®/Targinact®, which is a prolonged-release formulation of oxycodone and naloxone at a 2:1 ratio. In one of the Phase 3 studies involving 322 patients randomized to double-blind treatment, two patients reported adverse events (AEs) that were considered by the investigators to be related to opioid withdrawal. A second Phase 3 study in 278 patients found four cases of AEs considered to be related to opioid withdrawal that were reported in the oxycodone PR group, but none in the oxycodone PR/naloxone PR group. The data generated in these pivotal studies investigating Targin®/Targinact® confirmed that the addition of naloxone did not negatively affect analgesic efficacy of the opioid. The lack of an antagonizing effect of naloxone on opioid-induced analgesia is further supported by the results of a large, prospective, multicenter, observational study performed in 7,836 patients. In this study, only 6 (0.08%) individuals reported symptoms suggestive of opioid withdrawal (Section 3.1.3) during treatment with Targin®.

NLX PR Tablet Dosing and Study Design

Develco has formulated NLX PR Tablets to be titrated in each patient individually to a safe and effective dose. There is no convincing data to support the hypothesis that a fixed ratio of opioid:naloxone will be optimal in each and every patient. Depending on individual variability, the type of opioid, and the total daily opioid dose, different levels of naloxone may be tolerated by each patient. The protocols for Develco's EU studies are designed such that each patient is started at a low (6 mg daily) oral dose of NLX PR Tablets, which is then gradually increased to a maximum of 48 mg daily. Before any dose escalation, the patient is evaluated for increase in pain intensity, opioid rescue medication intake, and an assessment of opioid withdrawal symptoms using assessment tools that have been accepted by EU regulatory authorities. Any symptom of withdrawal or increase in pain intensity triggers a de-escalation of naloxone dose. This protocol reflects the intended use of the product, in which patients will be provided low levels of oral prolonged-release naloxone that are gradually titrated up to the optimal dose, with a maximum dose of 48 mg daily. By slowly increasing the dose of naloxone, the chance of inducing serious adverse events is minimized, and the effects of withdrawal can be reversed quickly (Section 2.5).

To date, Develco has not observed any withdrawal events reported during the double-blind treatment phase of its two ongoing EU safety and efficacy trials. As of 31 March 2014, a total of 10 incidences of withdrawal in 7 patients were reported in the two trials (206 total randomized patients), all during the 2-week opioid titration phase during which time the patient was not yet receiving naloxone. No withdrawal has been reported while being treated with NLX PR Tablets. Two adverse events belonging to the System Organ Class (SOC) "cardiac disorders" (palpitation, tachycardia) were reported, both occurring during the opioid titration phase. No cardiovascular events were reported in parallel with drug withdrawal (Section 2.5.1).

The design of Develco's US Phase 3 program is still in development. However, Develco intends to investigate NLX PR Tablets in patients on a range of opioid doses sufficient to represent the intended patient population. Develco also intends to include adequate opioid withdrawal assessments and analyses, which will be discussed and agreed upon with the FDA prior to initiation of the US Phase 3 studies. Additionally, the US Phase 3 program will include a plan to define, assess, and centrally adjudicate all MACE, including symptoms that may overlap with opioid withdrawal.

Postmarketing Data for Naloxone-Containing FDCs

At this stage of development, Develco does not have a large patient safety database to evaluate its own product for withdrawal or MACE. However, Develco has analyzed prescription data from the German statutory health insurances (Gesetzliche Kranken-versicherung; GKV; Section 4.3.2), as well as pharmacovigilance (PV) data from the World Health Organization (WHO) Global ICSR (individual case safety reports) Database System Programme (VigiBase®) and the German Federal Institute for Drugs and Medical Devices (BfArM) (Section 4.3.3). In Germany alone, between 2003 and 2012 more than 4 million patients have been exposed to oral prolonged-release naloxone products (e.g., Targin® and Valoron® N retard).

In evaluating the available safety databases, there was no specific, unexpected signal of higher reporting for cardiac events including MACE for oxycodone/naloxone (Targin®) or tilidine/naloxone (e.g., Valoron® N) compared to oxycodone or tilidine alone from either the analysis of Proportional Reporting Ratio (PRR)[1] for the VigiBase® data or from analysis of the BfArM safety database (Section 4.3.3).

In the BfArM safety database, the cumulative reporting frequency of adverse drug reactions for cardiac disorders for naloxone-containing oral products was low over the period from 2006 to 2012 (1 cardiac disorder per 100,000 patient years for tilidine/ naloxone; 14 cardiac disorders per 100,000 patient years for oxycodone/naloxone) (Section 4.3.3).

Develco has obtained additional postmarketing data and safety data from clinical trials for Targin®/Targinact® (Mundipharma). In its clinical trials involving approximately 4,000 patients randomized to Targin®, Mundipharma has observed no indication of increased risk of cardiovascular events in subjects treated with oxycodone/naloxone compared to subjects being treated with active or non-active comparators. Likewise, from the randomized double-blind clinical trial data, there is no indication supporting the hypothesis that naloxone, when included with oxycodone as a FDC product, induces cardiovascular events subsequent to the occurrence of drug withdrawal syndrome (Section 4.3.4).

[1] PRR is a statistic that functions much like an Odds Ratio to detect signals of disproportionate reporting. It is calculated by dividing the fraction of reports involving the reaction of interest for a given drug by the fraction of reports involving the reaction of interest for all other drugs in the database.

In its international drug safety database, Mundipharma identified 255 cases of drug withdrawal syndrome. Of these, 19 adverse events were falling under the SOCs “cardiac disorders”, “vascular disorders”, or “nervous system disorders”. None of the cardiac events entailed myocardial infarction or death (Section 4.3.4).

CONCLUSION

There is evidence from the publicly available literature and Develco’s own PK studies that there is very low systemic bioavailability of active drug due to high first-pass metabolism when prolonged-release naloxone is orally administered. Develco’s receptor affinity studies confirm that the major systemically available metabolite is inactive at opioid receptors. In Develco’s EU safety and efficacy studies, no signs of withdrawal have been noted during the treatment phase. A very low frequency of withdrawal was seen in the pivotal studies for oxycodone/naloxone (Targin®/Targinact®) and in its postmarketing data. The ability to titrate to a safe and effective dose is an additional safety aspect compared to Targin®’s fixed 2:1 ratio of oxycodone:naloxone. This will further reduce the risk for withdrawal and other systemic unwanted effects. Finally, pharmacovigilance data from FDC products containing tilidine/naloxone (e.g. Valoron® N) and oxycodone/naloxone (Targin®) compared to tilidine and oxycodone mono-preparations in large safety databases have revealed no evidence of increased cardiovascular events associated with naloxone (Section 4.3).

1 INTRODUCTION

Develco Pharma Schweiz AG (Develco) is developing Naloxone HCl Prolonged Release Tablets (NLX PR Tablets), a prolonged-release (PR) tablet formulation of naloxone for once or twice daily oral administration intended for the treatment of opioid-induced constipation (OIC). The formulation will be available in multiple strengths allowing for individual titration to a dose that provides relief of OIC symptoms while minimizing side effects. The product under development is intended to be freely combined with any opioid for the treatment of OIC.

Develco plans to submit an NDA for NLX PR Tablets in the US using the 505(b)(2) approval pathway.

Naloxone is a well-established active substance that is the most commonly used (parenteral) agent for complete or partial reversal of opioid depression and the treatment of opioid overdose. Several sublingual and oral fixed-dose combination (FDC) products containing naloxone have been marketed in the US and Europe for many years. Such compounds use naloxone as a deterrent for drug abuse. In addition, a FDC product containing oxycodone and naloxone (Targin®, Mundipharma GmbH, Germany; [14]) received marketing authorization in Germany in 2006 and subsequently in several other European countries. This product is approved for: "*severe pain, which can be adequately managed only with opioid analgesics. The opioid antagonist naloxone is added to counteract opioid-induced constipation by blocking the action of oxycodone at opioid receptors locally in the gut*" [15].

Naloxone is a semi-synthetic N-allyl derivative of oxymorphone and a specific competitive opioid receptor antagonist which has no agonistic or morphine-like properties. Naloxone has strong binding affinity to the opioid receptors inside and outside the central nervous system (CNS). It binds most strongly to the μ-opioid receptor but also shows antagonistic activity at the κ- and δ-opioid receptors [1] (Section 2.3). Under normal circumstances, naloxone has few to no pharmacological effects unless opioids with agonistic activity have been administered previously [2-5].

When administered orally, naloxone can reduce OIC via competitive antagonism at μ-opioid receptors in the gut. Although naloxone is readily absorbed from the gastro-intestinal (GI) tract, its oral bioavailability is extremely low (approximately 2%) due to extensive first-pass metabolism. The major metabolite formed by pre-systemic first-pass metabolism is naloxone-3-glucuronide, which shows negligible affinity to opioid receptors (Section 2.3). The laxative effect of naloxone is mediated via its local action in the gut without significant systemic antagonism of opioid analgesia. Hence, oral naloxone for the treatment of OIC can be considered a locally applied, locally acting μ-opioid receptor antagonist.

Opioids can delay gastric emptying, decrease peristalsis and slow bowel movement. Opioid-induced bowel dysfunction (OBD) involves not only constipation, but also a constellation of symptoms including incomplete evacuation, bloating, abdominal distension, and increased gastric reflux. Constipation is an almost inevitable consequence of opioid use in malignant and non-malignant disease states, and one of the side effects of opioids to which few patients

develop tolerance. Persistent and severe constipation appears to be the most common adverse effect of chronic opioid therapy and has been reported to occur in over 85% of patients. In some patients, OIC has been found to be dose-limiting [6-9]. According to another source, approximately 40% of patients receiving opioids for non-malignant pain experience OBD, including constipation (<3 bowel movements per week), symptoms of cramping, bloating and/or gastro-esophageal reflux [10].

Opioids appear to exert their effect on the GI tract primarily in the intestine, where peristaltic movements, which normally propel food down the intestine, are markedly diminished. Also, the tone of the intestine is greatly increased to the point where almost complete spastic paralysis of movement occurs. This combination of decreased propulsion and increased tone leads to a marked decrease in the movement of food through the intestine. This stasis is followed by a dehydration of the feces, which hardens the stool and further retards the advance of material. All these effects contribute to the constipating properties of opioids.

The effects of opioids on gastrointestinal motility and transit are thought to be predominantly mediated by the μ-opioid receptors. In the human gut, μ-opioid receptors are present in the enteric nervous system (ENS), i.e. in the submucosal plexus (Meissner's plexus) and the myenteric plexus (Auerbach's plexus) [7,9,11,12,72-75]. Thus, naloxone can act at the μ-opioid receptors after absorption from the gut lumen into the enteric tissues before entering the systemic circulation. Develco's prolonged-release oral formulation delivers naloxone directly to the gut wall, acting locally to antagonize the gut μ-opioid receptors and directly targeting the etiology of OIC. Upon approval, NLX PR Tablets will be the first oral mono-preparation of a locally acting μ-opioid receptor antagonist intended for the treatment of OIC.

2 NALOXONE HCL PR TABLETS

2.1 Drug Product

Naloxone (NLX) PR Tablets are characterized by the following features:

- Formulation: prolonged-release tablet
- Active substance: naloxone hydrochloride
- Mode of administration: oral
- Dosing interval: once daily (QD) or twice daily (BID)
- Strengths: 3 mg, 6 mg, 12 mg, 24 mg, 48 mg per tablet
- Proposed therapeutic dose range: 6 mg to 48 mg per day
- Indication: treatment of OIC

Since the formulation will be available in multiple strengths, this medicinal product should be titrated to an individual effective and safe dose, i.e. a dose that provides relief of OIC symptoms while minimizing side effects.

2.2 Development Program

Develco conducted a Pre-IND Meeting with the Division of Gastroenterology and Inborn Errors Products (DGIEP) on 13 August 2013. Develco also conducted Scientific Advice meetings with both the MHRA (UK, 03 February 2012) and the BfArM (Germany, 14 February 2012). Develco has completed *in vitro* ethanol susceptibility testing and clinical activities for two PK studies (Study 389B12 and Study 444B12) and initiated two safety and efficacy studies (Study 0176/DEV and Study 0177/DEV). All studies to date have been conducted in the EU. Based on feedback from MHRA and BfArM, nonclinical studies have not been required. However, the binding affinities of naloxone and naloxone-3-glucuronide to all three opioid receptor subtypes *in vitro* were investigated. The general clinical investigative plan agreed to with the MHRA and BfArM is outlined in Table 1.

Table 1: General Clinical Investigative Plan

Study ID	Study Design	Dosing Regimen and Route of Administration	Study Population	Status
		Clinical PK		
389B12	Single dose, randomized, open-label, five-treatment, five-period, five-sequence crossover at one study site	Single-dose oral administration of Naloxone HCl PR Tablets (3 mg, 6 mg, 24 mg, 48 mg, and 16 x 3 mg) under fasting conditions	15 healthy subjects	Completed
444B12	Single dose, randomized, open-label, three-treatment, three-period, six-sequence crossover at one study site	Single-dose oral administration of Naloxone HCl 48 mg PR Tablets under fed and fasting conditions Single-dose oral administration of naloxone 48 mg oral solution under fasting conditions	24 healthy subjects	Completed
TBD	Multiple dose, open-label, one-treatment, one-period, one-sequence study at one study site	Multiple-dose oral administration of Naloxone HCl 24 mg PR Tablets twice daily for 7 days under fasting conditions	16 healthy subjects	Planned
TBD	Multiple dose, open-label, one-treatment, one-period, one-sequence study at one study site	Multiple-dose oral administration of Naloxone HCl 48 mg PR Tablets once daily for 7 days under fasting conditions	16 healthy subjects	Planned
		Safety and efficacy		
0176/DEV	Randomized, double-blind, placebo-controlled, parallel-group design, multi-centre, dose-escalation Phase 3 trial to investigate the efficacy, safety, and tolerability of Naloxone HCl PR Tablets administered in a dose range of 3 mg to 24 mg twice daily in patients with opioid induced constipation	Naloxone HCl PR Tablets (3 mg, 6 mg, 12 mg, 24 mg), oral administration, twice daily, total daily dose: 6 - 48 mg	153 OIC patients	In-progress
0177/DEV	Randomized, double-blind, placebo-controlled, parallel-group design, multi-centre, dose-escalation Phase 3 trial to investigate the efficacy, safety, and tolerability of Naloxone HCl PR Tablets administered in a dose range of 6 mg to 48 mg once daily in patients with opioid induced constipation	Naloxone HCl PR Tablets (6 mg, 12 mg, 24 mg, 48 mg), oral administration, once daily, total daily dose: 6 - 48 mg	153 OIC patients	In-progress

The results from this clinical program will be used for an EU MAA, as agreed to with the EU regulatory bodies. The ongoing safety and efficacy studies 0176/DEV and 0177/DEV will be used as supportive evidence and will provide the basis for designing the pivotal US Phase 3 trials. Additional PK studies are also under consideration for a US NDA.

2.3 Binding Affinity

Develco performed radioligand binding assays to evaluate the binding affinity of naloxone and its major metabolite, naloxone-3-glucuronide to the μ-, κ-, and δ-opioid receptors. A summary of the results is presented in the table below.

Table 2: Binding Affinities of Naloxone and Naloxone-3-Glucuronide to the μ-, δ-, and κ-Opioid Receptors

	IC_{50} (μM)		
Substance	**μ**	**δ**	**κ**
Naloxone	0.011	0.59	0.031
Naloxone-3-Glucuronide	621	>1000*	>1000*
	K_i (μM)		
Substance	**μ**	**δ**	**κ**
Naloxone	0.00456	0.10	0.012
Naloxone-3-Glucuronide	252	n.d.	n.d.

n.d. – not detected.(Precise binding was below lowest limit of detection for the assay)

Consistent with previous reports, naloxone-3-glucuronide shows markedly lower affinity to the μ-opioid receptor compared to naloxone (the IC_{50} and K_i values are >50,000-fold higher compared to the parent compound indicating a >50,000-fold lower affinity). Naloxone-3-glucuronide also shows essentially no affinity at the δ- or κ-opioid receptor.

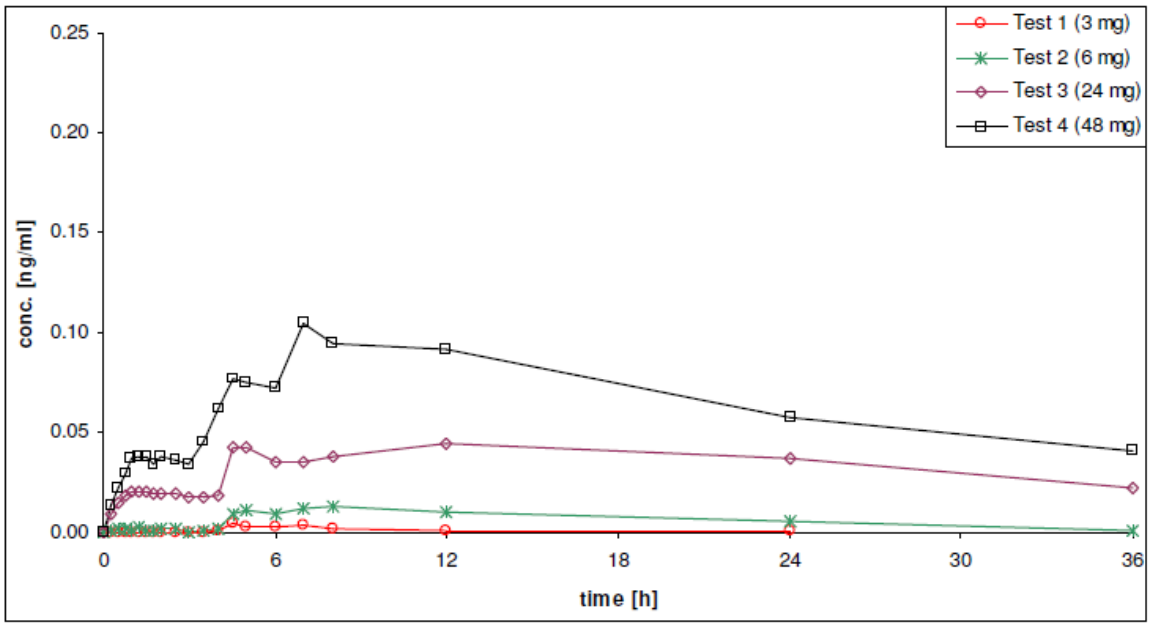
Naloxone has the highest affinity for the μ-opioid receptor and also shows significant binding to the κ- and δ-receptors. However, based on the K_i values, the binding affinity of naloxone is 3-fold lower at the κ-receptor and more than 20-fold lower at the δ-receptor compared with its affinity for the μ-receptor. Of note, the binding affinity of naloxone on the three opioid receptor subtypes falls within the range of other μ-opioid receptor antagonists for the treatment of OIC (Section 4.2.3).

2.4 Clinical Pharmacokinetic Studies

2.4.1 Dose Proportionality (Study 389B12)

Study 389B12 was a randomized, open label, crossover single-dose pharmacokinetics (PK) study with NLX PR Tablets (3 mg, 6 mg, 24 mg, and 48 mg) administered under fasting conditions in 15 healthy male and female subjects. The main objective of this trial was to investigate the dose proportionality of this formulation. Plasma concentrations of naloxone (NLX) and naloxone-3-glucuronide (NLX-3-G) were determined by a validated LC-MS/MS method. The lower limits of quantification (LLOQ) were 0.0100 ng/ml for NLX and 0.100 ng/ml for NLX-3-G.

(A) Naloxone



(B) Naloxone-3-Glucuronide

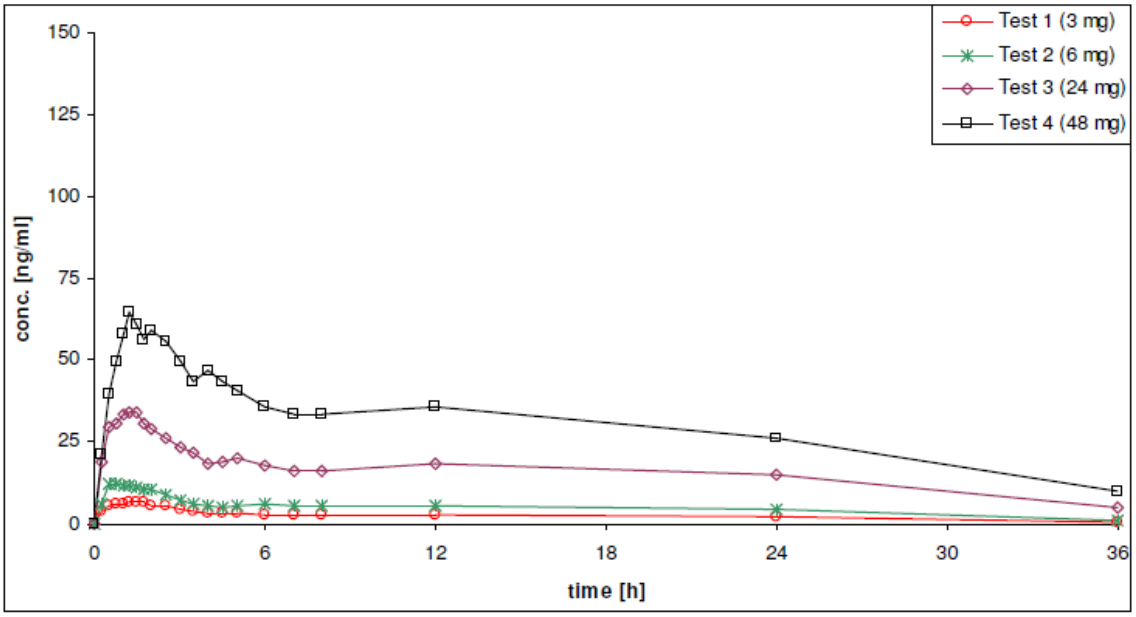


Figure 1: Mean (Arithmetic Mean) Plasma Concentration-Time Curves of (A) Naloxone and (B) Naloxone-3-Glucuronide after Single-Dose Administration under Fasting Conditions in Healthy Subjects (n=15).

The plasma concentration-time profiles for the parent compound naloxone were incomplete after administration of NLX 3 mg PR Tablets and NLX 6 mg PR Tablets. Naloxone plasma concentrations were below the LLOQ in most samples, consistent with the known high first-pass metabolism. Therefore, the PK parameters including $AUC_{(0-t)}$ and C_{max} could not be calculated reliably. The mean PK parameters for naloxone and naloxone-3-glucuronide are compiled in Table 3, including the relative ratios of NLX-3-G:NLX.

Table 3: Mean (±SD) PK Parameters of Naloxone and Naloxone-3-Glucuronide after Single-Dose Administration under Fasting Conditions in Healthy Subjects (n=15, Study 389B12)

	Naloxone HCl PR Tablets			
	3 mg	**6 mg**	**24 mg**	**48 mg**
Naloxone				
$AUC_{(0-t)}$ [ng/mL*h]	-	-	1.19 (0.65)	2.32 (1.24)
C_{max} [ng/mL]	0.008 (0.010)	0.025 (0.022)	0.067 (0.035)	0.150 (0.130)
t_{max} [h]	6.0 (4.0-8.0)	7.0 (0.5-24.0)	8.0 (0.5-36.0)	12.0 (4.0-36.0)
Naloxone-3-Glucuronide				
$AUC_{(0-t)}$ [ng/mL*h]	85.13 (26.30)	173.58 (62.58)	562.62 (234.77)	1,075.47 (413.95)
C_{max} [ng/mL]	8.08 (3.03)	14.77 (3.73)	41.57 (11.94)	90.30 (31.88)
t_{max} [h]	1.0 (0.25-4.0)	1.0 (0.25-6.0)	1.25 (0.5-5.0)	1.5 (0.5-4.0)
Ratio of Naloxone-3-Glucuronide:Naloxone				
$AUC_{(0-t)}$	--	--	473	464
C_{max}	1010	591	620	602

t_{max} values are given as median (range).

AUC not calculated for 3 mg and 6 mg because of incomplete plasma concentration-time profiles.

Dose proportionality was accepted if the differences in the dose-adjusted mean $AUC_{(0-t)}$ values were ≤25%. All calculated differences for dose-adjusted $AUC_{(0-t)}$ values were within ±25%. Therefore, based on $AUC_{(0-t)}$, dose proportionality could be concluded for naloxone (24 mg vs. 48 mg) and naloxone-3-glucuronide (for all dose levels).

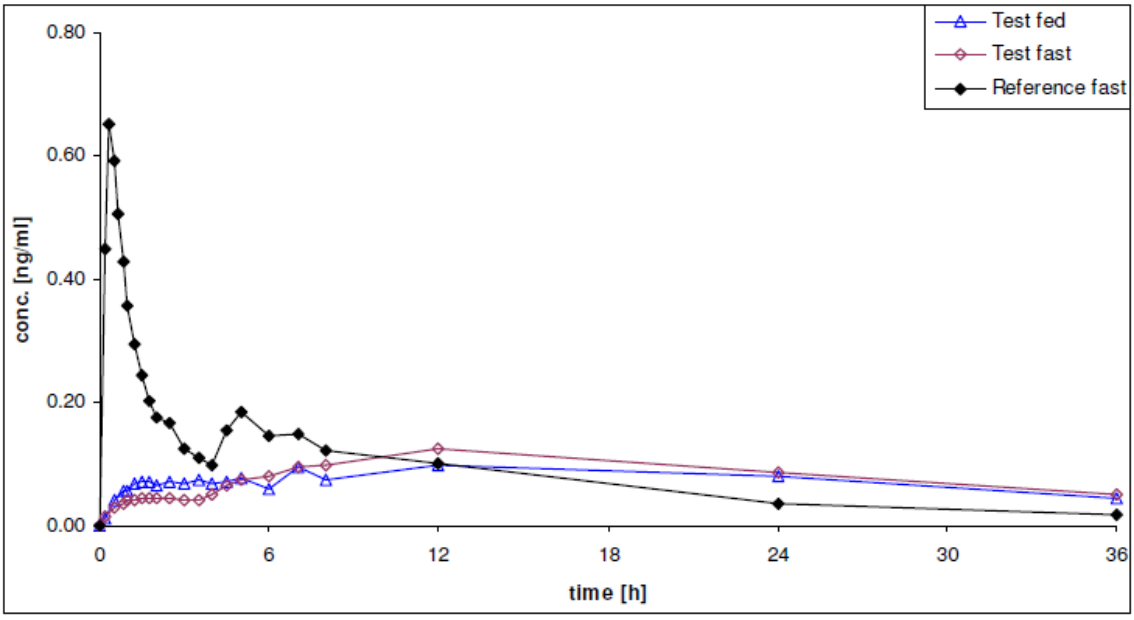
2.4.2 Food Effect (Study 444B12)

Study 444B12 was designed as a randomized, open-label, crossover single-dose study and investigated whether food has an effect on the *in vivo* performance (rate and extent of absorption) of the highest 48 mg strength of NLX PR Tablets. In this study which was conducted in 24 healthy male and female subjects, naloxone was also administered as an immediate-release oral solution (120 ml naloxone solution containing 48 mg naloxone

hydrochloride; reference product) under fasting conditions in order to characterize the prolonged-release properties of the new formulation.

Plasma concentrations of naloxone and naloxone-3-glucuronide were determined by a LC-MS/MS method (LLOQ 0.005 ng/ml for NLX and 0.100 ng/ml for NLX-3-G) The mean plasma concentration-time profiles of naloxone and naloxone-3-glucuronide after single-dose administration of 48 mg NLX PR Tablets under fasted and fed conditions and 48 mg naloxone given as oral solution in the fasted state are illustrated in the following figure.

(A) Naloxone



(B) Naloxone-3-Glucuronide

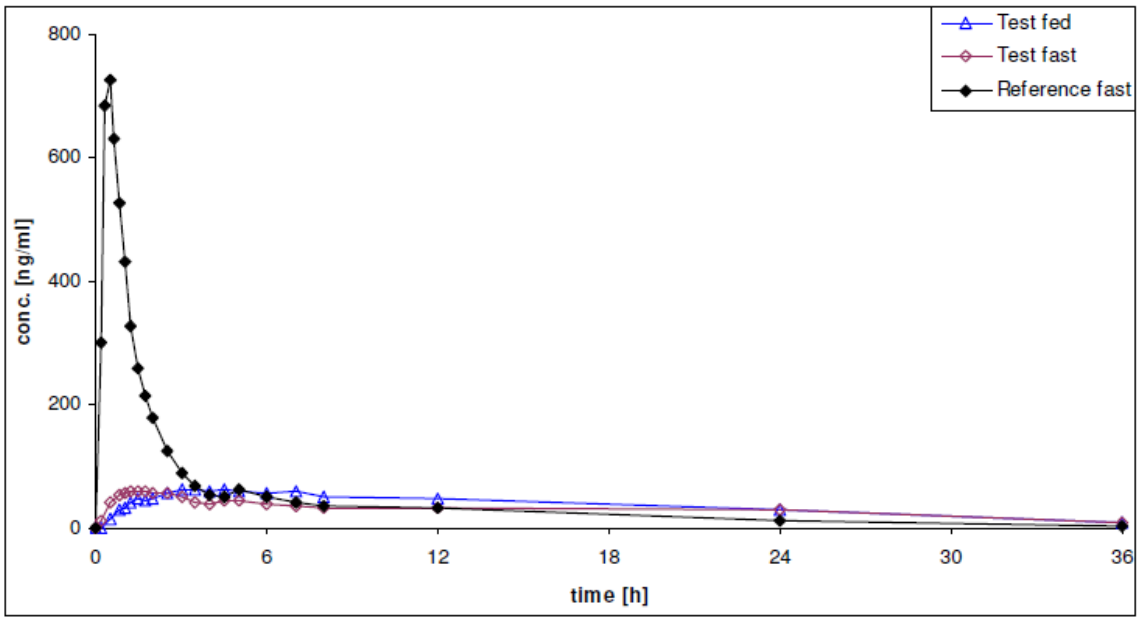


Figure 2: Mean (Arithmetic Mean) Plasma Concentration-Time Curves of (A) Naloxone and (B) Naloxone-3-Glucuronide after Single-Dose Administration of Naloxone 48 mg PR Tablets (Test, Fasted and Fed) and 48 mg Naloxone as Oral Solution (Reference, Fasted) in Healthy Subjects (n=24).

The following table summarizes the mean PK parameters for naloxone and naloxone-3-glucuronide.

Table 4: Mean (±SD) PK Parameters of Naloxone and Naloxone-3-Glucuronide after Single-Dose Administration of Naloxone 48 mg PR Tablets (Fasted and Fed) and 48 mg Naloxone as Oral Solution (Fasted) in Healthy Subjects (n=24, Study 444B12)

	NLX 48 mg PRT (fed)	NLX 48 mg PRT (fasted)	48 mg oral solution (fasted)
Naloxone			
$AUC_{(0-t)}$ [ng/mL*h]	2.73 (2.29)	2.97 (4.53)	3.18 (2.56)
C_{max} [ng/mL]	0.16 (0.15)	0.17 (0.29)	0.73 (0.22)
t_{max} [h]	6.50 (0.50-36.0)	6.00 (0.833-36.0)	0.417 (0.167-5.00)
Naloxone-3-Glucuronide			
$AUC_{(0-t)}$ [ng/mL*h]	1,301.37 (333.99)	1,081.64 (319.63)	1,676.72 (428.81)
$AUC_{(0-\infty)}$ [ng/mL*h]	1,495.28 (499.68)	1,298.23 (511.34)	1,726.59 (462.50)
C_{max} [ng/mL]	85.77 (21.13)	80.69 (23.85)	785.76 (231.15)
t_{max} [h]	3.25 (0.833-8.00)	1.375 (0.167-5.00)	0.50 (0.333-1.25)
$t_{½}$ [h]	11.23 (3.88)	12.81 (4.86)	7.70 (2.02)
Ratio of Naloxone-3-Glucuronide:Naloxone			
$AUC_{(0-t)}$	477	364	527
C_{max}	536	475	1076

t_{max} values are given as median (range).

Elimination half-life ($t_{½}$) not calculated for naloxone because of insufficient plasma concentration-time profiles in the elimination phase

No food interaction could be observed for the rate (C_{max}) and extent of absorption (AUC) of the parent compound naloxone from NLX PR Tablets. For the metabolite naloxone-3-glucuronide, a slight food effect was seen for the extent of absorption (increase in mean AUC by about 20%).

In the comparative bioavailability assessment of naloxone from the 48 mg NLX PR Tablets versus the oral solution (both administered under fasting conditions), the mean ratio for $AUC_{(0-t)}$ reached 76.0% (90% CI: 67.08-86.11%). Comparable figures were found for naloxone-3-glucuronide with a mean ratio for $AUC_{(0-t)}$ of 63.7% (90% CI: 57.34-70.72%). Hence, systemic exposure to naloxone and naloxone-3-glucuronide was significantly lower (by approximately 24% and 36%) after administration of the NLX PR Tablet as compared to the oral solution.

In general, the plasma concentration-time profiles of the parent compound and the metabolite following administration of the prolonged-release tablet formulation differ considerably compared to those observed for the immediate-release oral solution. In line with the prolonged-release characteristics of NLX PR Tablets, peak plasma concentrations of naloxone and naloxone-3-glucuronide reached only about 25% and 10% of the peak level observed for the immediate-release oral solution. Furthermore, the NLX PR Tablet formulation showed a gradual increase in plasma concentrations with delayed occurrence of C_{max} values and overall a comparably flat concentration-time curve.

2.4.3 Safety Assessments in the Clinical Pharmacokinetics Studies

In the two single-dose PK studies with Naloxone HCl PR Tablets, no safety issues occurred. These two studies were conducted in healthy subjects who were not using an opioid. In the dose-proportionality study (Study 389B12, section 2.4.1), single-doses of 3 mg to 48 mg naloxone were well tolerated. Only headache was reported (five times). In the food-effect study (Study 444B12, Section 2.4.2), subjects received Naloxone HCl 48 mg PR Tablets (test product) under fasting and fed conditions and an oral solution containing 48 mg naloxone (reference product). Both, the tablet formulation and the oral solution were well tolerated. There were 10 adverse events observed in 6 subjects (5 AEs in each group). These were headache (7, test and reference product), nausea (2, test and reference product) and vomiting (1, reference product).

2.5 Ongoing Clinical Safety and Efficacy Studies

The two safety and efficacy studies (Study 0176/DEV and Study 0177/DEV) in progress in Europe are identical regarding study design, study population, study medication, endpoints etc. Both studies are randomized, double-blind, placebo-controlled, parallel-group design, multi-center, dose-escalation studies to investigate the efficacy, safety, and tolerability of NLX PR Tablets in a dose range of 6 mg to 48 mg per day in adult patients with OIC. The only difference between the trials is that Naloxone HCl PR Tablets are administered twice daily (BID) in Study 0176/DEV, while a once daily (QD) dosing regimen is used in Study 0177/DEV. Patients are eligible for inclusion if they have a documented history of chronic severe non-malignant pain requiring around-the-clock opioid therapy and a documented history of OIC.

Both studies consist of six phases:

- **Screening phase**
- Open-label **opioid titration phase**. Patients will discontinue their previous opioid treatment and will be randomized (1:1) to either oxycodone or hydromorphone trial medication. Dosage adjustment will be performed until adequate analgesia is achieved

with a stable opioid dose. After completion of the opioid titration phase the trial opioid dose may not be changed.

- Single-blind Naloxone HCl PR Placebo **run-in phase** with fixed duration of 2 weeks. Patients will discontinue their previous laxative medication and will receive NLX PR Placebo. If OIC (according to modified Rome III criteria and Bowel Function Index [BFI]) and adequate and stable analgesia are confirmed at the end of the 2-week run-in phase, patients will be randomized (2:1) to double-blind treatment with NLX PR Tablets or placebo.
- Double-blind **dose-escalation/treatment phase** with a duration of 12 weeks. Patients will start with the lowest total daily dose of 6 mg naloxone and will be treated on this dose level for 2 weeks. After 2 weeks, the dose will be escalated to 12 mg naloxone per day for a further 2 weeks. Each further escalation step (dose level of 24 mg and 48 mg naloxone per day) will last for at least 2 weeks. The decision of naloxone dose-escalation, de-escalation or treatment failure will be based on the evaluation of pain control and tolerability. Once the individual final naloxone dose level has been established based on the effect on bowel function, the patient will continue to take this naloxone dose until end of Week 12, i.e. for at least 4 weeks.
- Double-blind **extension phase** with a duration of 2 weeks. Patients will be randomized (1:1) to abrupt or tapered cessation of naloxone in order to assess potential differences.
- **Follow-up phase**: 9 to 14 days after end of the extension phase, patients will undergo the final physical examination and laboratory tests.

The flow chart of Study 0176/DEV is presented in Appendix 1.

In both studies, it is planned to randomize 153 patients to the double-blind treatment phase.

The efficacy endpoints comprise assessments of: Bowel Function Index (BFI; change from baseline is the primary endpoint); number of bowel movements (BMs), spontaneous bowel movements (SBMs), and complete spontaneous bowel movements (CSBMs); Bristol Stool Form Scale (BSFS); Symptoms of Defecation Score; Patient Assessment of Constipation - Symptoms (PAC-SYM), Patient Assessment of Constipation – Quality of Life (PAC-QOL); and the use of laxative rescue medication.

Safety will be assessed by evaluation of pain intensity, use of opioid rescue medication, modified Subjective Opioid Withdrawal Scale (SOWS), clinical laboratory parameters, vital signs and physical examination as well as AE monitoring.

The primary objective of the studies is to demonstrate that treatment with Naloxone HCl PR Tablets is superior to placebo in the improvement/reversal of OIC as determined by the BFI.

2.5.1 Safety Assessments in the Safety and Efficacy Studies

Study 0176/DEV (Eudra CT number: 2012-003218-14, cf. Section 2.5) is a randomized, double-blind, placebo-controlled, parallel-group design, multi-centre, dose-escalation trial. NLX PR Tablets are administered in a dose range of 3 mg to 24 mg twice daily in patients with OIC. It is planned to randomize 153 subjects to the double-blind treatment phase. The first patient in was on 12-Mar-2013. As of 31-March-2014, 152 patients were randomized, and 61 completed the trial. Eight cases of "drug withdrawal syndrome" (preferred term) were reported in 5 patients as adverse event , none of them related to naloxone as all cases occurred in the open-label opioid titration phase (i.e. before start of double-blind treatment with either naloxone or placebo). Two adverse events belonging to the System Organ Class (SOC) "cardiac disorders" (palpitation, tachycardia) were reported, both occurred during the open-label opioid titration phase. In all 8 cases of "drug withdrawal syndrome", no additional cardiovascular event was reported in parallel.

Study 0177/DEV (Eudra CT number 2012-004311-31, cf. Section 2.5) is similarly designed with the exception that NLX PR Tablets are given once daily but in the same dose per day (6 mg to 48 mg once daily). It is planned to randomize 153 subjects to the double-blind treatment phase. The first patient in was on 24-Jun-2013. As of 31-March-2014, 54 patients were randomized, and 14 completed the trial. Two (2) patients experienced the adverse event "drug withdrawal syndrome" (preferred term), both not related to naloxone as they occurred in the open-label opioid titration phase (i.e. before start of double-blind treatment with either naloxone or placebo). No adverse event belonging to the SOC "cardiac disorders" has been reported in this trial so far. Furthermore, no cardiovascular event was reported in combination with the two cases of "drug withdrawal syndrome". No serious adverse event was reported so far in this ongoing trial.

Heart rate and blood pressure are only measured at screening, at the end of the opioid titration phase, at the end of the NLX Placebo run-in phase, at the end of the double-blind treatment phase, and at follow-up. The data are still blinded at this time.

Although there is limited clinical data regarding NLX PR Tablets available, all respective data do not indicate a concern regarding overall patient safety, and specifically, no safety signal regarding cardiac events is identified either alone or in combination with drug withdrawal syndrome.

3 NALOXONE – WELL-ESTABLISHED ACTIVE SUBSTANCE

Naloxone has been used in various formulations world-wide and adequate nonclinical and clinical data exist in the literature and from previously approved drugs to evaluate its pharmacodynamic, pharmacokinetic, and toxicological properties.

Naloxone has been marketed under various trade names (e.g., Narcan®) for decades as a solution for intravenous (i.v.), intramuscular (i.m.), or subcutaneous (s.c.) injection for complete or partial reversal of opioid depression, including respiratory depression, induced by natural and synthetic opioids. It may also be used for the diagnosis of suspected acute opioid overdose and to counteract respiratory and other CNS depression in newborns resulting from the administration of analgesics to the mother during childbirth [16-18].

Mono-preparations of naloxone for the above mentioned indications are currently only available as parenteral solutions. However, naloxone is a component of several approved oral fixed-dose combination (FDC) products (EU and US). These products are compiled below.

Table 5: Marketed Oral Fixed Dose Combination Products Containing Naloxone

Brand name	Active ingredients	Strengths	Mode of administration and dosage	Indication(s)	Ref.
SUBOXONE®, sublingual tablet (approval date: Oct 2002 in US, discontinued; Sept 2006 in EU)	***Buprenorphine*** HCl / ***Naloxone*** HCl dihydrate	2 mg / 0.5 mg 8 mg / 2 mg (ratio 4 : 1)	Sublingually; 12 - 16 mg buprenorphine as single daily dose ***Naloxone:*** ***3 - 4 mg per day***	Opioid drug dependence	[19]
SUBOXONE®, sublingual film (approval date: Aug 2012 in US)	***Buprenorphine*** HCl / ***Naloxone*** HCl dihydrate	2 mg / 0.5 mg 4 mg / 1 mg 8 mg / 2 mg 12 mg / 3 mg (ratio 4 : 1)	Sublingually; 12 - 16 mg buprenorphine as single daily dose ***Naloxone:*** ***3 - 4 mg per day***	Opioid drug dependence	[93]
TALWIN® Nx, tablets (approval date: Dec 1982 in US; product was discontinued in 2009; but since 1997 several generic products are on the US market)	***Pentazocine*** HCl / ***Naloxone*** HCl	50 mg / 0.5 mg (ratio 100 : 1)	Oral; 50 mg pentazocine every 3 - 4 hours, maximum 600 mg per day ***Naloxone:*** ***3 - 4 mg per day (maximum 6 mg)***	Moderate to severe pain	[69]

Brand name	Active ingredients	Strengths	Mode of administration and dosage	Indication(s)	Ref.
VALORON® N, oral solution (approval date: Jun 1978 in Germany)	***Tilidine*** HCl / ***Naloxone*** HCl	50 mg / 4 mg / 0.72 ml (ratio 12.5 : 1)	Oral; up to 50 - 100 mg tilidine every 4 hours ***Naloxone:*** ***24 - 48 mg per day (maximum 48 mg)***	Severe to very severe pain	[21]
VALORON® N retard, tablets (approval date: Dec 1997 in Germany)	***Tilidine*** phosphate / ***Naloxone*** HCl	50 mg / 4 mg 100 mg / 8 mg 150 mg / 12 mg 200 mg /16 mg (ratio 12.5 : 1)	Oral; 50 - 300 mg tilidine twice daily dose ***Naloxone:*** ***8 - 48 mg per day (maximum 48 mg; in individual cases exceeding the maximum daily dose may be required)***	Severe to very severe pain	[20]
TARGIN® TARGINACT® PR tablets (approval date: May 2006 in Germany; and afterwards in several other member states of the EU via mutual recognition procedures)	***Oxycodone*** HCl / ***Naloxone*** HCl dihydrate	5 mg / 2.5 mg 10 mg / 5 mg 20 mg / 10 mg 40 mg /20 mg (ratio 2 : 1)	Oral; initial 10 mg oxycodone twice daily dose, maximum 80 mg per day ***Naloxone:*** ***initial 10 mg per day (maximum 40 mg)***	Severe pain, which can be adequately managed only with opioids, with the naloxone component being added to counteract OIC	[14,15]

The rationale for adding naloxone to Suboxone®, Talwin®Nx and its generic versions, Valoron® N oral solution, and Valoron® N retard (prolonged-release tablets) was to help limit diversion of the opioids for misuse by the intravenous route. In Targin®, the addition of naloxone is intended specifically to counteract the effects of oxycodone in causing OIC.

In the US, naloxone is combined with buprenorphine (Suboxone®) for sublingual administration for the maintenance treatment of opioid dependence [19] and with pentazocine (generic products of Talwin®Nx) for the treatment of moderate-to-severe pain [69]. In combination with tilidine, naloxone for oral administration has been marketed in Germany for more than 30 years for the treatment of severe pain without limitation of duration of use [20,21]. The same holds true for an oral fixed-dose combination product containing oxycodone and naloxone indicated for the treatment of severe pain (Targin®/Targinact®) which has been approved in 2006 in Germany and in many other European countries in 2008/2009. The maximum recommended dose of naloxone from Targin®/Targinact®, i.e., 40 mg naloxone HCl, closely approximates the proposed maximum daily dose of 48 mg naloxone HCl for the product under development [14,15]. Of note, the

proposed maximum daily dose of 48 mg naloxone HCl for the Naloxone HCl PR Tablets is identical to the recommended maximum daily dose of naloxone HCl contained in Valoron® N oral solution and Valoron® N retard, products which are widely used in Germany for the treatment of acute and chronic pain [20, 21].

3.1 NALOXONE – PUBLICLY AVAILABLE DATA

Due to its well-established clinical use, the pharmacodynamic, pharmacokinetic, and toxicological properties of naloxone are well known.

3.1.1 Nonclinical Data

Naloxone has shown relatively low acute toxicity. LD_{50} values of 150 ± 5 mg/kg and 109 ± 4 mg/kg have been reported in mice and rats, respectively, following i.v. administration. After s.c. injection, the LD_{50} was 260 mg/kg in mice [16]. The maximum tolerated dose (MTD) of oral naloxone for mice was approximately 600 mg/kg, with animals showing mild-to-severe tremors at that dose level. One of 5 male rats receiving naloxone at a dose of 800 mg/kg died, indicating that LD_{50} is slightly higher. The LD_{50} for oral naloxone in rabbits was around 2,500 mg/kg [30].

In a repeat-dose study in rats receiving naloxone by oral gavage for 3 months, only a few clinical signs (decreased activity, reduction in weight gain) were observed, even at relatively high doses. The no observed adverse event level (NOAEL) was 50 mg/kg/day. In another repeat-dose study, rats received naloxone up to 100 mg/kg/day incorporated into their diet over a period of 2 years. The study indicated a NOAEL of 20 mg/kg/day. A NOAEL of 75 mg/kg/day was found in dogs dosed with oral naloxone for 39 weeks [30].

3.1.2 Clinical Pharmacokinetics

3.1.2.1 Absorption

Following oral administration naloxone is rapidly and readily absorbed (75%) from the GI tract but undergoes extensive intestinal and hepatic first-pass metabolism. The drug is almost completely metabolized by the liver before reaching the systemic circulation resulting in an oral bioavailability of 2-3% after intake of therapeutic doses [1,5,14,15,18,31], with some studies showing bioavailability of less than 2% [23]. A study using a very high oral dose of 500 mg immediate-release naloxone in healthy volunteers confirmed the drug's rapid absorption and the considerable first-pass metabolism. The maximum plasma concentration (C_{max}) of naloxone was 7 ng/ml and was observed 0.5 h after dosing. Plasma concentrations of the main metabolite naloxone-3-glucuronide were approximately 700-times higher than that of the parent compound [24].

Single-Dose and Multiple-Dose Pharmacokinetics

An open-label, randomized, crossover single-dose study compared the pharmacokinetics of both components of the fixed combination product of prolonged-release oxycodone/naloxone (administered either as 4 x 10 mg/5 mg, 2 x 20 mg/10 mg, or 1 x 40 mg/20 mg) with the free combination of oxycodone PR 40 mg plus naloxone PR 20 mg in 28 healthy subjects.

The plasma concentrations of naloxone and its main metabolite naloxone-3-glucuronide were determined; however, the concentrations of the former were very low. For naloxone, the mean AUC_{0-t} ranged from 0.84 to 0.97 pg/ml*h, the C_{max} from 0.07 to 0.08 pg/ml, and the median t_{max} from 1.0 to 5.0 hours. For naloxone-3-glucuronide, the AUC_{0-t} was in a range of 520.1 to 539.9 ng/ml*h, the C_{max} ranged from 61.95 to 63.62 ng/ml, and the median t_{max} from 0.5 to 1.0 hours. The apparent terminal half-life calculated for naloxone-3-glucuronide was approximately 8 hours [27].

A more recently published open-label, 7-treatment, 5-period, randomized incomplete cross-over study assessed the absolute bioavailability of oral PR naloxone tablets (5 mg, 20 mg, 40 mg, 80 mg, and 120 mg) following single-dose administration in 28 healthy subjects. Following oral dosing of 5 mg, 20 mg, 40 mg, 80 mg, and 120 mg, the mean AUC_{0-t} was 158.2, 1,331.1, 2,868.2, 5,983.5, and 8.939.8 pg/ml*h and the mean C_{max} was 32.45, 98.57, 204.69, 406.59, and 632.98 pg/ml, respectively. The mean absolute bioavailability of naloxone from the orally administered PR tablets in comparison with 1 mg naloxone given by an i.v. infusion over 30 minutes (based on dose-adjusted AUC_{0-t} values) ranged from 0.9% for the 5 mg dose to 2.0% for the 40 mg, 80 mg, and 120 mg doses. After oral dosing, C_{max} values reached only up to 17% of that observed following i.v. infusion of 1 mg naloxone. Median t_{max} was 5 hours for all oral doses except the 120 mg dose (1.75 h). The pharmacokinetics of oral naloxone were linear across the dose range studied [23].

The multiple-dose pharmacokinetics of naloxone have been investigated in 18 healthy male subjects who received sustained-release tablets of tilidine/naloxone 100 mg/8 mg 12-hourly and an oral solution of tilidine/naloxone 50 mg/4 mg every 6 hours. Under steady state conditions, the mean AUC of total naloxone was 241.9 ng/ml*h after treatment with the tablet formulation compared with 260.0 ng/ml*h for the oral solution. The mean C_{max} value at steady-state was lower after administration of the sustained-release tablet compared with the oral solution (20.2 vs. 31.5 ng/ml) and median t_{max} was longer (3.0 vs. 0.5 h). The apparent terminal $t_{½}$ was 6.7 h for the tablet formulation compared with 5.9 h for the solution [26].

3.1.2.2 Distribution

Naloxone is a highly lipophilic compound and is therefore rapidly and extensively distributed into body fluids and tissues including the brain. Naloxone rapidly disappears from the serum in man and the initial distribution phase has a half-life of approximately 4 minutes following i.v. administration [2,28]. Based on animal studies the rapid onset of the antagonistic action

of naloxone can be related to its rapid entry into the brain due to its high lipid solubility, whereas its short duration of action may result from its rapid egress from the brain [28]. Serum protein binding is approximately 32 to 45%. The serum half-life of the initial distribution phase was 4.7 minutes following i.v. administration. The volume of distribution has been reported to be 200 l [1,3,5,18,28]. Naloxone crosses the placenta, but serum concentrations in the fetus do not reach maternal levels [5].

3.1.2.3 Metabolism

Naloxone is metabolized in the liver primarily by conjugation with glucuronic acid with naloxone-3-glucuronide as the major metabolite. Other metabolites are produced in smaller amounts, such as by N-dealkylation and reduction of the 6-keto group. In humans, reduction of the 6-keto group results in formation of the 6-β-naloxole metabolite, which has antagonistic activity [5,18,29].

3.1.2.4 Excretion

In adults, the elimination half-life is approximately 1 to 1.5 hours (range 30 to 100 minutes) after parenteral administration [4,5,18]. After oral single-dose administration of naloxone prolonged-release tablets (5, 20, 40, 80, and 120 mg), the half-life of naloxone ranged from 11.3 h (80 mg dose) to 16.6 h (20 mg dose) in healthy subjects [23]. Excretion of naloxone and its metabolites begins rapidly with 24 - 37% of the administered dose appearing in the urine in the first 6 hours. About 60% of the total dose is excreted in the urine within 72 hours as conjugated metabolites with naloxone-3-glucuronide representing the major metabolite [3,28,29].

3.1.2.5 Special Populations

Information on alterations in pharmacokinetics of naloxone when administered orally to elderly subjects or patients with impaired renal or hepatic function can primarily be derived from studies conducted during the Targin®/Targinact® clinical trial program, which is described below.

Elderly Patients

The results of a multiple-dose study conducted in healthy elderly patients (≥65 years) vs. healthy younger subjects (18 - 45 years) revealed that the plasma naloxone concentrations are higher in the elderly group after dosing with Targin®. On average, for the AUC over the dosing interval (AUC_τ), C_{max}, and C_{min}, there was an increase to 182%, 173%, and 317%, respectively, in elderly compared with younger subjects [14,15,30].

Patients with Renal Impairment

Although the prescribing information for Valoron® N retard (tilidine/naloxone prolonged-release tablets) [20] states that no dose adjustment is necessary in patients with impaired renal function, the data from a PK study conducted with the combination product containing oxycodone and naloxone (Targin®/Targinact®) revealed that systemic availability of naloxone is markedly increased in this patient population. There was an average increase in AUC_{0-t} of naloxone of 2,850%, 3,910%, and 7,612% in patients with mild, moderate, and severe impairment of renal function, respectively, as compared to healthy subjects. For C_{max}, there was an increase of 1,076%, 858%, and 1,675% in patients with mild, moderate, and severe impairment of renal function, respectively, as compared to healthy subjects [14,15,30].

Patients with Hepatic Impairment

Studies on the impact of impaired hepatic function on the pharmacokinetics of naloxone do not provide consistent results. Only a minor increase in AUC and C_{max} of total naloxone was found in a study conducted in 8 patients with severe hepatic impairment (Child Pugh score ≥7, mono-ethyl-glycine-xylidide 15-min test value <50 ng/ml) treated with tilidine/naloxone oral solution at a dose of 100 mg/8 mg [31]. In contrast, another trial in patients with mild, moderate, and severe hepatic impairment (Child Pugh grading 5 - 6, 7 - 9, and 10 - 15, respectively) who received a single dose of oxycodone/naloxone 10 mg/5 mg reported an increase of 411%, 11,518%, and 10,666% in AUC_{0-t} and of 193%, 5,292%, and 5,252% in C_{max}, respectively, [14,15,30].

3.1.3 Safety and Efficacy of Naloxone in OIC

The use of oral naloxone in OIC has obtained increased attention in recent years. An early study performed in healthy subjects found that naloxone administered orally at doses of 16 to 32 mg antagonized the delay in oro-coecal transit time induced by the peripherally acting opioid loperamide [33]. Likewise, naloxone (10 mg twice daily dose) given orally for 9 days to 12 healthy male volunteers shortened the mean whole-gut transit time and was able to antagonize the effect of codeine on GI transit [34].

Efficacy

Several early case reports and small-scale studies in patients have shown oral immediate-release naloxone to be effective in reversing opioid-induced delays in GI transit times and producing relief of OIC [6,8,35,36].

The Phase 2 and Phase 3 clinical trials conducted with the fixed-dose combination product Targin®/Targinact® containing prolonged-release oxycodone and naloxone (ratio 2:1) consistently demonstrated the efficacy of naloxone in treating OIC. The three pivotal Phase 3 studies involved more than 1,100 patients with chronic moderate-to-severe non-malignant

pain requiring continuous opioid therapy and suffering from OIC randomized to double-blind treatment, Oxycodone PR/naloxone PR significantly improved symptoms of OIC as shown by a decrease in the Bowel Function Index (BFI) and an increase in the number of CSBMs per week studies [30, 37-39,61]. Statistically significant and clinically relevant improvements in BFI score were observed in oxycodone PR/naloxone PR treated patients by week 1 and at every subsequent time point during the 12-week, double-blind phase [39]. Adding naloxone to oxycodone did not affect pain control; pain intensity remained stable throughout the 12-week double-blind treatment phase [37,38].

Sander-Kiesling and co-workers conducted an analysis of the long-term efficacy and safety of oxycodone PR/naloxone PR in 637 non-malignant pain patients included in two Phase 3 trials [37,61] who entered the 52-week open-label extension phases. The mean BFI score decreased from an initial value of 35.6 to 20.6 after 12 months. In patients who had received oxycodone PR/naloxone PR in the preceding double-blind phase, the BFI score showed only a slight reduction from 28.7 to 26.2 at the end of the 52-week extension phase indicating that the maximum therapeutic effect was achieved during double-blind treatment and maintained over the period of 12 months [70].

The safety and efficacy of oxycodone PR/naloxone PR was assessed under conditions of daily practice in a large prospective, observational study involving 7,836 chronic pain patients. Patients were observed for 4 weeks. The pain causing underlying disease was musculoskeletal (85.9%) and malignant disease (17.3%). The majority of patients were pretreated with opioids (74.6%), while 25.1% of patients were opioid-naïve. Bowel function improved significantly, as demonstrated by an overall decrease in BFI score from 38.2 to 15.1 after 4 weeks. As expected, the effect was more pronounced in patients with opioid pre-treatment. Quality of life assessed by the Brief Pain Inventory BPI-SF improved by 43% [62].

A more recent randomized, double-blind, active-controlled, parallel-group, multicenter trial investigated the efficacy and safety of oxycodone PR/naloxone PR in 185 patients with chronic malignant pain. Patients were randomly assigned to 4-week treatment with either oxycodone PR/naloxone PR (up to 120 mg/60 mg per day) or oxycodone PR (up to 120 mg per day). After 4 weeks of treatment, mean BFI score (difference -11.14, 95% CI: -19.03 to -3.24, $p<0.01$), PAC-SYM total symptom score ($p<0.014$), and frequency of symptoms score ($p<0.01$) were significantly lower in the oxycodone PR/naloxone PR group compared to the oxycodone PR group [71].

Safety

Naloxone is generally considered a safe drug and has no or only occasional minor effects even when given in higher doses in the absence of opioid drugs [5]. The incidence of adverse events (AEs) reported in the Phase 3 studies conducted with the fixed dose combination of oxycodone PR/naloxone PR was either comparable or slightly higher than that reported under treatment with oxycodone PR alone. The three pivotal Phase 3 studies investigating the FDC of oxycodone PR/naloxone PR which included 1,064 patients randomized to double-blind treatment revealed that GI disorders were the most commonly reported AEs. Overall, the

incidence of serious adverse events was very low and no serious cardiovascular AEs, especially no myocardial infarction or other serious ischemic cardiac events, were mentioned. Only a few cases of AEs considered to be related to opioid withdrawal occurring with similar frequency in the oxycodone PR/naloxone PR group and the oxycodone PR group were reported [30,37,38,61].

In the study published by Ahmedzai et al. which was conducted in chronic cancer pain patients who were randomized to receive up to 120 mg oxycodone PR or 120 mg/60 mg oxycodone PR/naloxone PR, the incidence of AEs was generally similar for both groups. The most frequently reported AEs were GI disorders and "general disorders and administration site conditions". The incidence of GI disorders was slightly higher in patients treated with oxycodone PR/naloxone PR compared to those treated with oxycodone PR alone (37.0% vs. 30.4%). There were no clinically important changes in vital signs and ECG assessments. Opioid withdrawal scores (SOWS) remained stable throughout the study and were even somewhat lower for oxycodone PR/naloxone PR (6.64 vs. 8.01) and oxycodone PR (7.29 vs. 8.90) compared to baseline [71].

The data generated in the pivotal studies and in the study in chronic cancer pain patients investigating the fixed dose combination product confirmed that addition of naloxone did not negatively affect analgesic efficacy of the opioid [37-61,71].

The lack of an antagonizing effect of naloxone on opioid-induced analgesia is further supported by the results of a large, prospective, multicenter, observational study performed in 7,836 patients. In this study, only 6 (0.08%) individuals reported symptoms suggestive of opioid withdrawal during treatment with Targin® [62].

Recently published data collected during the optional open-label extension phase of two Phase 3 studies demonstrated the long-term tolerability and safety of the oxycodone PR/naloxone PR combination. Based on the reported AEs (most frequently GI disorders), clinical laboratory reports, vital signs, and ECG data, oxycodone PR/naloxone PR was considered to have a favorable tolerability profile during long-term use [63].

4 CARDIOVASCULAR SAFETY OF ORAL NALOXONE

Recently, questions have been raised whether long-term use of μ-opioid receptor antagonists in opioid-induced constipation (OIC) is associated with an increase in serious cardiovascular adverse events. In order to assess and analyze a potential cardiac safety concern related to the long-term use of naloxone in the treatment of OIC, Develco has critically reviewed the data available in the European Union with special emphasis on Germany, which represents the main market for the oral FDC products containing naloxone. In the following, Develco initially provides theoretical considerations while considering the receptor binding of naloxone, the related signal transduction and its bioavailability. Subsequently, Develco reviews the well-established long-term use of orally administered naloxone by an analysis of German prescription data and presents an assessment on cardiovascular safety signals based on pharmacovigilance data from the WHO Collaborating Centre for International Drug Monitoring (Uppsala Monitoring Centre) and the Safety Database at the German Federal Institute for Drugs and Medical Devices (BfArM). Finally, Develco shares postmarketing data and safety data from clinical trials for the FDC product containing oxycodone and naloxone (Targin®/Targinact®) from Mundipharma.

4.1 Opioid Receptors and Cardiovascular Function

Opioid-receptors are involved in cardiovascular regulation in a very complex way, acting on different levels, i.e., they may exert locally- or centrally-mediated effects via directly or indirectly interacting with other receptor systems or signal transduction pathways. The *in vivo* antagonistic effects of naloxone on cardiovascular function are not uniform and their clinical implications remain uncertain.

In general, opioid receptors involved in cardiovascular regulation have been localized centrally in the cardiovascular and respiratory centers of the hypothalamus/brainstem, and peripherally in cardiac myocytes, blood vessels, nerve terminals and adrenal medulla. Myocardial binding studies have shown that δ - and κ-opioid receptors are present on adult ventricular myocytes of the rat, and furthermore, κ- and δ-opioid receptors are located on the ventricular cardiac sarcolemma. Developmental studies demonstrate the presence of δ- and κ-opioid receptors in adult rat heart, whereas, only μ- and κ-opioid receptors were present in neonatal rat hearts, suggesting a development-dependent expression of δ-opioid receptors in the heart [40]. In functional contractile studies, the presence of κ- and δ-opioid receptors was demonstrated in adult rat ventricular cardiac myocytes, but not μ-opioid receptors. In support of the functional studies, no μ-opioid receptor gene expression was detected, whereas the δ-opioid receptor transcript was the predominant form detected in the rat heart [40,41].

An intrinsic opioid receptor system in the heart may contribute to functional changes in normal and diseased myocardium. A number of physiological and pathological cardio-vascular responses of δ-opioid receptor stimulation include attenuation of cardiac adrenergic responses, inhibition of vagally-mediated bradycardia induced by acetylcholine release, suppression of the baroreceptor mechanism and reduction in cardiac performance. Likewise,

it has been reported that the activation of δ-opioid receptors inhibits ß-adrenergic receptor-mediated positive inotropic effects [41,42]. The κ-opioid receptor activation has been implicated in arrhythmogenesis in normal and ischemic hearts, in influencing cardiac function, and in inhibiting norepinephrine release. Thus, activation of the δ- and the κ-opioid receptors have the theoretic potential to result in both cardioprotective and cardiotoxic effects in man. The lack of μ-opioid receptor activity in the heart has been supported by a number of receptor-binding studies in ventricular myocytes [41].

The influence of opioid receptors on cardiac function has been further implicated for ischemic preconditioning (IPC). IPC is the phenomenon whereby brief sub-lethal periods of ischemia protect the heart against a more sustained ischemic event. Literature references have that the cardioprotection by IPC is triggered by δ-opioid receptors [42,43] as well as κ-opioid receptors [42,44].

Published data indicate that the effects of naloxone on the heart are mediated via the CNS as well as by direct cardiac effects [40,45-48]. There is evidence suggesting that the antagonism of opioid receptors with naloxone may diminish IPC in humans [49] and rats [50] via blockade of δ- and κ-opioid receptors [40], although the clinical relevance of these phenomena to spontaneous myocardial infarction has not been established.

Naloxone´s action on the molecular level reveals that the drug is antagonistic to all subtypes of opioid receptors, with strongest affinity to the μ-opioid receptor and weaker affinity to the κ- and δ-opioid receptors (Section 2.3). Its influence on the cardiovascular system has been predominately attributed to the κ- and δ-opioid receptors mediating direct cardiac effects as well as within a cross-talk of ß-adrenergic and opioid receptors.

Central opioid receptor antagonism and cardiovascular effects

Blockade of μ-opioid receptors in the CNS can lead to partial or complete withdrawal in individuals dependent on opioids. Withdrawal is associated with increased sympathetic outflow from the CNS. The sympathetic nervous system response includes cardiovascular effects such as tachycardia and elevated blood pressure and consequently increased myocardial oxygen demand and consumption. Thus, opioid-receptor antagonistic drugs crossing the blood-brain-barrier may increase sympathetic tone and indirectly affect the cardiovascular system.

Summary of involvement of opioid receptors and adverse cardiac events

Based on the on the presence of opioid receptors in the myocardium and CNS, it is theoretically plausible that naloxone may exert cardiovascular effects if systemic concentrations are sufficient, such as when naloxone is administered parenterally. Naloxone has greatest affinity for the μ-opioid receptor, which is not of relevance regarding peripheral opioid-receptor-mediated cardiovascular effects, while its affinity is lower for the κ- and δ-opioid receptors. Activation of δ- and κ-opioid receptors in the myocardium might result in

both cardioprotective and cardiotoxic effects. Binding of naloxone to central μ-opioid receptors may precipitate withdrawal thereby indirectly affecting the cardiovascular system.

However, the association between withdrawal and increased risk of MACE has not been clearly established. A case-control study of 81 opioid-addicted patients hospitalized for cardiovascular evaluation found no difference in myocardial infarction rates between those with and without acute opioid-withdrawal [51].

In any event, potential cardiovascular effects induced by centrally or peripherally acting opioid receptor antagonists require sufficient systemic bioavailability of the drug. Although naloxone is rapidly and readily absorbed from the GI tract, its oral bioavailability only amounts to approximately 2% due to the considerable pre-systemic metabolism thereby forming predominantly naloxone-3-glucuronide. Naloxone-3-glucuronide shows negligible receptor affinity at the opioid receptors (Section 2.3). Consequently, systemic exposure of naloxone after oral administration is very low and plasma concentrations of the active parent compound are highly unlikely to achieve levels thought to be associated with clinically relevant cardiovascular effects.

4.2 Naloxone HCl PR Tablets in Comparison to other μ-Opioid Receptor Antagonists used in OIC

4.2.1 Distinguishing Features of Naloxone HCl PR Tablets

Naloxone is a well established drug substance with thoroughly characterized toxicological, pharmacokinetic, and pharmacodynamic properties, as well as decades of clinical use. Furthermore, Naloxone HCl PR Tablets will be available in multiple strengths allowing for a careful titration to an individually effective and safe dose considering both, relief of OIC symptoms and the occurrence of (systemic) side effects. The defining characteristics of NLX PR Tablets are:

- Locally acting on μ-opioid receptors in the gut.
- Low systemic availability of naloxone due to high first-pass metabolism.
- Prolonged-release formulation resulting in reduced naloxone peak plasma concentrations and flat concentration-time profiles.
- Titration dosing and mono-preparation to allow for individualized dosing of each patient to a safe and effective dose.

In principle, there are two approaches to effectively relieve OIC and other manifestations of OBD without interfering with centrally-mediated analgesia:

- Orally administered opioid antagonists with limited systemic absorption, such as naloxone.

- Peripherally acting μ-opioid receptor antagonists with no or only minor penetration across the blood-brain-barrier.

Oral prolonged-release naloxone in the treatment of OIC belongs to the first approach and can be considered a locally applied, locally acting drug. Therefore, the drug exerts its therapeutic effect by antagonism of opioid actions at the μ-opioid receptors locally in the gut. Systemic availability of naloxone is neither required nor desired for its therapeutic use in OIC. Indeed, due to extensive pre-systemic metabolism, the systemic exposure of naloxone is typically very low. The major inactive metabolite, naloxone-3-glucuronide, represents almost the entire drug-related material absorbed from the GI tract and reaching the systemic circulation.

4.2.2 Bioavailability

Oral prolonged-release naloxone

The pharmacokinetics of naloxone are described in more detail in Section 2.4 and 3.1.2 of this document. Naloxone is rapidly and readily (~75%) absorbed from the gastrointestinal tract. However, naloxone is subject to considerable first-pass metabolism and is rapidly and almost completely inactivated following oral administration. It is metabolized in the intestine and liver, mainly by glucuronide conjugation, with naloxone-3-glucuronide as the major metabolite [5,18,23,29].

The absolute bioavailabilities of prolonged-release naloxone from oral doses of 5 mg to 120 mg were recently studied by Smith et al. in healthy subjects [23]. The mean absolute bioavailability was very low, ranging from 0.9% for the 5 mg dose to 2% for the 40, 80 and 120 mg doses. These data are in good agreement with earlier reports [1,5,14,15,18] and the results from own PK studies (Section 2.4).

The bioavailability and the plasma concentration-time curve of naloxone differ remarkably depending on the route of administration and the pharmaceutical formulation. Compared to oral administration, all other forms of application, i.e. intravenous, intramuscular, intranasal etc., result in complete or considerably higher systemic exposure to naloxone due to circumvention of first-pass metabolism. When oral dosage forms are taken into account, the pharmaceutical formulation is similarly critical for the rate and extent of absorption of naloxone. As demonstrated in Section 2.4.2, the Naloxone HCl PR Tablet had significantly lower bioavailability and particularly lower peak plasma concentrations of naloxone compared with the immediate-release oral solution.

Peripherally acting μ-opioid receptor antagonists

Naloxegol (NKTR-118) is a new oral peripherally acting μ-opioid receptor antagonist for which the US FDA has accepted the NDA in November 2013. Naloxegol is a PEGylated derivative of naloxone. The PEGylation of naloxone alters its distribution (reduced CNS penetration) and metabolism (reduced first-pass effect) while its opioid antagonistic properties are retained . Naloxegol was found to have substantial oral bioavailability with rapid absorption (t_{max} 0.75 h) and an extended half-life of 11 h. Plasma concentrations of the metabolite naloxegol-glucuronide were approximately 100-fold less than plasma naloxegol concentrations. After multiple-dose administration of 25 mg twice daily (the therapeutic dose is 12.5 and 25 mg once daily), C_{max} and AUC_{0-12h} for naloxegol reached 96.9 ng/mL and 363.9 ng/mL*h, respectively [76-80].

Methylnaltrexone (Relistor®), a quaternary derivative of naltrexone, is administered as a subcutaneous (s.c.) injection with a usual schedule of one dose every other day. After s.c. injection, methylnaltrexone is absorbed rapidly, with peak plasma concentrations occurring at about 0.5 h. The absolute bioavailability of methylnaltrexone administered subcutaneously versus intravenous injection is 82%. Methylnaltrexone is metabolized to a modest extent; all metabolites have low systemic exposure. The terminal half-life of methylnaltrexone is about 8 h. Following a single s.c. dose of 0.15 mg/kg methylnaltrexone (equals to the therapeutic dose of 12 mg for a patient with a body weight of 80 kg), C_{max} was 117 ng/mL and AUC_{0-24h} 175 ng/mL*h [81,82].

Alvimopan (Entereg®): following oral administration of alvimopan capsules at the therapeutic dose of 12 mg, peak plasma alvimopan concentration was on average 9.9 ng/mL and occurred at approx. 2 h. The mean absolute bioavailability was estimated to be 6% (range 1% to 19%). The biliary secretion is considered the primary pathway for elimination of alvimopan. Unabsorbed drug and biliary excreted unchanged alvimopan is metabolized by gut microflora to an amide hydrolysis compound (ADL 08-0011) which is an equipotent antagonist at μ-opioid receptors. This metabolite is either excreted in the feces or absorbed from the gut lumen and enters the systemic circulation. The systemic exposure of this active metabolite has been reported to be up to 20-fold higher than that of the parent compound alvimopan. After multiple-dose administration of 6 mg alvimopan, the mean AUC of ADL 08-0011 reached 422.5 ng/mL*h compared with 23.3 ng/mL*h for the parent compound. The plasma concentrations of ADL 08-0011 accumulated 6- to 9-fold after 5 days of dosing. The mean terminal elimination half-life of alvimopan after multiple oral doses ranged from 10 to 17 hours and that of ADL 08-0011 from 10 to 18 hours [83-86].

4.2.3 Binding Affinity and Potency

Binding affinity studies performed during the development of alvimopan included also other opioid receptor antagonists and thus allow for a direct comparison. Radioligand binding assays using cloned human opioid receptor subtypes revealed the following results for

alvimopan, ADL 08-0011 (active metabolite of alvimopan), methylnaltrexone, and naloxone [87]:

Table 6: Binding Affinity of Different Opioid Receptor Antagonists to Opioid Receptor Subtypes

Substance	K_i (nM)		
	μ	**δ**	**κ**
Alvimopan	0.44	10	99.6
ADL 08-0011	0.81	110	290
Methylnaltrexone	30	870	101
Naloxone	3.3	33	8.1

Alvimopan had the highest affinity for the μ-receptor compared to all other compounds and has also significant affinity for the δ-receptor. ADL 08-0011 is approximately equipotent to alvimopan at the μ-receptor, but is more selective with lower affinities to the δ- and κ-receptors. Methylnaltrexone showed the lowest affinity for the μ-receptor compared to the other compounds. While the affinity of methylnaltrexone is highest for the μ-receptor, significant binding was also detected at the κ-receptor. Compared to alvimopan and methylnaltrexone, naloxone had intermediate affinity to the μ-receptor. Naloxone binds most strongly to the μ-receptor, but has also significant affinity to the κ- and δ-receptors [87].

In vitro antagonism of opioid receptor-mediated [^{35}S]GTPγS binding was also investigated for alvimopan, methylnaltrexone, and naloxone. The potencies of the antagonists were assessed by their ability to inhibit agonist-stimulated [^{35}S]GTPγS binding to membranes containing cloned human μ-, δ-, and κ-opioid receptors. Alvimopan, methylnaltrexone, and naloxone were competitive antagonists at all three opioid-receptor subtypes. Alvimopan inhibited agonist-stimulated binding mediated by the μ-receptor with 5- and 118-fold greater potency than naloxone and methylnaltrexone, respectively. Likewise, alvimopan was 8-fold and 480-fold more potent than naloxone and methylnaltrexone at inhibiting agonist-stimulated δ-mediated binding. Alvimopan inhibited agonist-stimulated binding mediated by the κ-opioid receptor with similar potency compared to naloxone and 28-fold greater potency compared to methylnaltrexone. Among all substances tested, methylnaltrexone had the lowest potency at all opioid receptor subtypes [87].

The K_i value for naloxegol for the μ-opioid receptor was 33.8 nM compared to 1.68 nM for naloxone. Therefore, naloxegol had 20-fold lower affinity at the μ-opioid receptor than naloxone. Currently no information is publically available concerning the binding affinity of naloxegol for the δ- and κ-opioid receptors.

4.2.4 Relationship between Potency and Peak Exposure

In order to translate *in vitro* potency of opioid receptor antagonists into *in vivo* effects in terms of systemic antagonistic action, drug exposure must reach or exceed a certain level. To assess the relationship between the drug's peak plasma concentration achieved *in vivo* in humans and the potency of different μ-opioid receptor antagonists at the opioid-receptor subtypes obtained from *in vitro* studies, i.e. their IC_{50} values, the ratio between IC_{50} and C_{max} value was calculated.

The IC_{50}/C_{max} ratio is an established measure to estimate the therapeutic and/or toxicity index of a given drug. The *in vitro-in vivo* correlation of IC_{50} and maximum systemic concentration is, for instance, frequently used to assess the potential of a compound for drug-drug interactions. For example, the IC_{50}/C_{max} ratio is often determined to evaluate the influence of drugs on the cardiac human *ether-a-go-go*-related gene (hERG) potassium current and thus, their ability to produce QT prolongation [88,90]. Higher IC_{50}/C_{max} ratios correspond to a greater margin of safety, whereas lower values are predictive of clinical risk for arrhythmia. For instance, in the opioid agonist class, morphine has a hERG IC_{50}/C_{max} of >400, whereas methadone, a drug with substantial proarrhythmic potential, has a value of 2.7 [94].

The IC_{50}/C_{max} ratios for selected opioid antagonists used for OIC are depicted below in Table 7.

Table 7: IC_{50}/C_{max} Ratios for Different μ-Opioid Receptor Antagonists for the Opioid Receptor Subtypes

Substance	C_{max} [ng/mL]	IC_{50} [nM]	Ratio IC_{50}/C_{max}	Ref.
μ-opioid receptor				
Naloxone PR Tablets (48 mg p.o.)	0.15	8.1	54.00	[study 389B12, 87]
Alvimopan (12 mg p.o.)	9.9	1.7	0.17	[86, 87]
Methylnaltrexone (0.15 mg/kg s.c.)	117	200	1.71	[81, 87]
δ-opioid receptor				
Naloxone PR Tablets (48 mg p.o.)	0.15	380	2,533.33	[study 389B12, 87]
Alvimopan (12 mg p.o.)	9.9	50	5.05	[86, 87]
Methylnaltrexone (0.15 mg/kg s.c.)	117	24,000	205,13	[81, 87]
κ-opioid receptor				
Naloxone PR Tablets (48 mg p.o.)	0.15	45	300.00	[study 389B12, 87]
Alvimopan (12 mg p.o.)	9.9	53	5.35	[86, 87]
Methylnaltrexone (0.15 mg/kg s.c.)	117	1,500	12.82	[81, 87]

Naloxone, when administered orally at the highest dose of 48 mg currently tested, showed the highest IC_{50}/C_{max} ratios at all opioid receptor subtypes compared with alvimopan and methylnaltrexone. At the μ-opioid receptor, the IC_{50}/C_{max} ratio for naloxone was more than 300-fold and more than 30-fold higher than the ratio for alvimopan and methylnaltrexone, respectively. Similarly, the IC_{50}/C_{max} ratio for naloxone at both δ-opioid and κ-opioid receptors were substantially higher than the ratios for alvimopan and methylnaltrexone. Considering the IC_{50}/C_{max} ratios found for naloxone at all opioid receptor subtypes, therefore, it is highly unlikely that naloxone plasma concentrations achieved after oral administration of NLX PR Tablets (even at the highest dose) are sufficient to result in systemic antagonistic effects.

SUMMARY

Oral prolonged-released naloxone in the treatment of OIC can be considered a locally applied, locally acting drug. The drug exerts its therapeutic effect by antagonism of opioid actions at the μ-receptors locally in the gut. Therefore, systemic availability of naloxone is neither required nor desired for its therapeutic use in OIC. Indeed, due to extensive pre-systemic metabolism, the systemic exposure of naloxone is typically very low. The major inactive metabolite, naloxone-3-glucuronide, represents almost the entire drug-related material absorbed from the GI tract and reaching the systemic circulation.

Other μ-opioid receptor antagonists developed for the treatment of OIC enter the systemic circulation in substantial concentrations either as parent compound and/or active metabolite to exert their pharmacodynamic effects as summarized in the table below.

Table 8: Absolute Bioavailability and Contribution of Major Metabolite to Systemic Exposure for Oral Naloxone and Other μ-Opioid Receptor Antagonists

	NLX (p.o.)	MNTX (s.c.)	Alvimopan (p.o.)	Naloxegol (p.o.)
Absolute Bioavailablity	≤2%	82%	6%	Substantial*
Major metabolite?	YES (NLX-3-G)	NO	YES (ADL 08-001)	NO
Major metabolite active?	NO (>50,000 lower affinity than NLX)	n.a.	YES (equipotent)	n.a.
AUC ratio of parent compound : major metabolite	1:364** (parent:inactive M)	n.a.	1:~20 (parent:active M)	n.a.

NLX = naloxone; NLX-3-G = naloxone-3-glucuronide; MNTX = methylnaltrexone, n.a. = not applicable

* no absolute BA value available

** from study 444B12 (AUC ratio after single-dose of 48 mg under fasting conditions)

As outlined above, all opioid-receptor antagonists approved or currently developed for the treatment of OIC or comparable disorders including naloxone have highest binding affinity to the μ-opioid receptor. Naloxone shows also significant binding to the κ- and δ-receptors. Nonetheless, all other compounds similarly bind with relevant affinity to at least one further opioid-receptor subtype (δ- and/or κ-receptor). Therefore, all these drugs display only relative receptor selectivity. Naloxone has intermediate binding affinity and potency at opioid-receptors compared to the other compounds. Due to the extremely low systemic availability of naloxone when administered orally as prolonged-release formulation, the IC_{50}/C_{max} ratio for naloxone is exceedingly higher than for alvimopan and methylnaltrexone.

4.3 Postmarketing Data for Naloxone-Containing FDCs

4.3.1 Significance of Spontaneous Reporting Systems

Pharmacovigilance systems rely heavily on spontaneous (or voluntary) reporting in which suspected adverse drug reactions (ADRs) are reported to either a national coordinating center, competent authorities or marketing authorization holders by health care professionals, marketing authorization holders or directly by patients. Of all the sources of data for drug safety monitoring, the spontaneous reporting systems provide the highest volume of information and have utility in the early detection of patient safety issues related either to the products themselves or to their respective use. Since spontaneous reporting is dependent on the initiative and motivation of the reporters, the data collected by this method may be incomplete and do not permit calculation of incidence rates for specific ADRs. Thus, underreporting is a significant limitation of this method. However, an advantage of spontaneous reporting systems is their potential for early detection of safety signals in broad healthcare settings [66,68].

Concerning the pharmacovigilance data on naloxone-containing FDCs presented below, it must be emphasized that due to the fact that mono-preparations (of the opioid component contained in the FDCs, namely tilidine and oxycodone) are also marketed, a comparison group is available. Therefore one may analyze data from spontaneous reporting systems for both groups to assess whether there is a signal for the occurrence of adverse drug reactions such as cardiac disorders specifically for the naloxone-containing FDCs. Under these circumstances, the problem of underreporting may be less likely to bias the assessment of cardiovascular safety signals for the naloxone-containing FDCs as both products (FDC and mono-preparation) can be expected to be at least similarly prone to underreporting.

4.3.2 Patient Use of Oral Naloxone in Germany

The prolonged-release FDC products of tilidine plus naloxone (e.g. Valoron® N retard) and oxycodone plus naloxone (Targin®) are widely prescribed for pain management. Prescription data from the German statutory health insurances (Gesetzliche Krankenversicherung; GKV) which include data recording on anonymous patient ID level (= patient tracking) were analyzed for both products for the period from 01 July 2003 (or market entry of Targin® in October 2006) and 31 December 2011. Approximately 90% of the German population are insured by statutory health insurances (~70 million), while 10% are insured by private health insurances.

Projection of prescription data from the German GKV to the total German population demonstrate that:

- The total number of patients entered into therapy with immediate- or prolonged-release FDCs of tilidine plus naloxone (e.g. Valoron® N retard) in Germany between July 2003 and December 2011 accounts for 3.8 million patients;
- The total number of patients entered into therapy with the prolonged-release FDC of oxycodone plus naloxone (Targin®) in Germany between October 2006 and December 2011 accounts for 510,000 patients.

The FDC products coupled with prolonged-release naloxone have been used extensively in Germany. Especially the highest strengths of tilidine plus naloxone (200 mg tilidine/ 16 mg naloxone) and oxycodone plus naloxone (40 mg oxycodone/20 mg naloxone) were used for long-term treatment, with an average duration of therapy of 200 and 300 days, respectively.

Altogether, in Germany alone, more than 4 million patients have been exposed to oral immediate- or prolonged-release naloxone by the end of 2011.

4.3.3 Analysis of Cardiovascular Safety Signals

EVALUATION OF DATA FROM THE WHO COLLABORATING CENTRE FOR INTERNATIONAL DRUG MONITORING

Introduction

Due to the fact that the oral oxycodone/naloxone FDC product has been on the European market for seven years and used by a large number of patients, its cardiac safety may be evaluated in greater detail using inferential statistical methods. In addition, the data for the tilidine/naloxone combination products and the mono-preparations of oxycodone and tilidine will be presented. The evaluation of the proportional reporting ratio (PRR) is a useful and well established tool to describe signals of disproportionate reporting (SDR) . The PRR is a statistical parameter akin to an odds ratio that is used to summarize the extent to which a particular adverse event is observed for individuals taking a specific drug, compared to the frequency at which the same adverse event occurs for patients taking some other drug (or who are taking any drug in a specified population). This method is generally less biased than simple comparisons of report counts. The PRR makes the assumption that when a SDR (involving a particular adverse event) is identified for a medicinal product, this adverse event is reported relatively more frequently in association with this medicinal product than with other medicinal products [56,57]. The PRR will typically be calculated using a surveillance database in which reports of adverse events from a variety of drugs are recorded.

The evaluation of the PRR has the advantage that exposure data are not necessary for such assessment, which are often not generally accessible. A limitation of the PRR evaluation, which is a limitation of all analyses dealing with spontaneous reports, is, amongst other factors, under-reporting rate [53,54]. The PRR was calculated based on the principles described in the “Guideline on the use of statistical signal detection methods in the

Eudravigilance data analysis system" (EMEA/ 106464/2006 Rev. 1; June 2008; see [56,57]). The main focus was on events that included preferred terms from the System Organ Class (SOC) "cardiac disorders". The data are compared to oxycodone and tilidine mono-substance medicinal products. For all drugs, the route of administration was either oral or unknown.

To assess whether there might be a SDR with regard to cardiac side effects of oxycodone plus naloxone and tilidine plus naloxone, data from the WHO Collaborating Centre for International Drug Monitoring (Uppsala Monitoring Centre [VigiBase®]) was used. VigiBase® consists of reports of adverse reactions received from the member states since 1968 (currently 112 countries worldwide). The VigiBase® data resource is the largest and most comprehensive in the world. By April 2013 over 8 million reports were contained in the database[2].

The WHO Collaborating Centre for International Drug Monitoring explicitly informs that the information contained in VigiBase® is derived from various sources (voluntary and regulatory) and that the reports in many instances describe no more than suspicions which have arisen from observation of an unexpected or unwanted event. In most instances it cannot be proven that a pharmaceutical product or ingredient is causally related to a specific adverse event. Therefore, all pharmacovigilance data should be interpreted with care and in context with other clinical data for compounds of interest. [55].

Results

Cardiac disorders

The numbers of cases with ADRs from the SOC "cardiac disorders", from all other SOCs, and the total number of ADRs registered for oxycodone, oxycodone plus naloxone, tilidine, and tilidine plus naloxone in comparison to all other medicinal products (providing the basis for the calculation of the PRRs) is presented in Table A.1, Appendix 2.

Two approaches can be applied to detect a SDR for a given drug-event combination. A statistical signal is seen if all of the following criteria are fulfilled for each method [56]:

PRR is displayed with its 95% CI:	**PRR is displayed with the χ^2-statistic:**
• the lower bound of the 95% CI ≥1; • the number of individual cases ≥3	• the PRR ≥2 • the χ^2 ≥4 • the number of individual cases ≥3

[2] http://www.who-umc.org/DynPage.aspx?id=98082&mn1=7347&mn2=7252&mn3=7322&mn4=7326

Table 9 lists the results of the PRRs per mono-preparation versus drug combination regarding events of the SOC "cardiac disorders".

Table 9: Reaction Monitoring for Oxycodone versus Oxycodone/Naloxone and Tilidine versus Tilidine/Naloxone for the SOC "Cardiac Disorders" (PRR, 95% CI, χ^2)

	Oxycodone		Oxycodone/Naloxone	
Reaction (MedDRA)	**PRR (95% CI)**	**X^2**	**PRR (95% CI)**	**X^2**
SOC cardiac disorders	2.38 (2.28 - 2.49)	1,504.08	1.45 (1.09 – 1.92)	6.366
	Tilidine		**Tilidine/Naloxone**	
Reaction (MedDRA)	**PRR (95% CI)**	**X^2**	**PRR (95% CI)**	**X^2**
SOC cardiac disorders	1.13 (0.67 – 1.91)	0.21	0.92 (0.65 – 1.31)	0.21

X^2 Pearson chi-square

For the oxycodone mono-preparation, a statistically significant signal was seen with regard to the occurrence of cardiac disorder events when applying both methods. This seems to be caused by a high number of cardiac and cardio-respiratory arrest cases (1,101 ADRs), (acute) myocardial infarction (99 ADRs), and tachycardia cases (204 ADRs).

In the oxycodone plus naloxone group, the PRR is <2 suggesting the absence of a prominent signal of disproportionate reporting (SDR). However, the lower bound of the 95% CI is >1 and the χ^2-statistic is >4. For the tilidine plus naloxone group none of the SDR criteria are fulfilled. Overall, the criteria are numerically more favorable for the FDC combination products and the number of cases with ADRs from the SOC "cardiac disorders" is very low.

This is particularly reassuring given the extensive utilization and mean exposure periods for these products. The ADRs included myocardial infarction and acute myocardial infarction (i.e. 6 cases in the oxycodone plus naloxone group and one case in the tilidine plus naloxone group). Out of the 6 cases of myocardial infarction that occurred in the oxycodone plus naloxone group, 2 cases were assessed as being not drug-related. In addition, in some of these cases other concurrent drugs could have contributed to the event as well. The case of myocardial infarction in the tilidine plus naloxone group was accompanied by the ADR "overdose" which might contribute as additional risk factor.

A list of all ADRs from the SOC "cardiac disorders" occurring under the oral mono-preparations oxycodone and tilidine as well as under the FDCs oxycodone plus naloxone and tilidine plus naloxone is given in Appendix 2 (Tables A.2–A.5).The mono-preparations (pure opioid agonist) were dominated by "cardiac" and "cardiorespiratory arrest" which are the

primary established risks for potent opioids [88]. ADRs were substantially less frequently reported for both FDCs.

Withdrawal syndrome alone and withdrawal syndrome combined with cardiac disorders

Beside cardiac disorders events, a focus was also placed on the occurrence of the ADRs "withdrawal syndrome". Therefore, for all four drug categories (i.e. oxycodone, oxycodone plus naloxone, tilidine, tilidine plus naloxone) all cases with the ADR "withdrawal syndrome" (MedDRA preferred term, PT) were cross-checked with events from the SOC "cardiac disorders".

The VigiBase® received 10,866 case reports of adverse events for oral oxycodone mono-preparations in the period 1998-2012. During that time period, 124 unique reports of "withdrawal " and 8 of those concurrently listed cardiac disorders: tachycardia, heart rate decreased, heart attack, arrhythmia, cardiac disorder, heart rate irregular (one case each), palpitations (2 cases). In the oxycodone plus naloxone group, there were 23 cases of "withdrawal syndrome" (among 453 ADRs in total) reported in the period 2006-2012. Of those, 4 cases also reported cardiac events (cardiac arrhythmia, cardiac arrest, tachycardia, and cyanosis).

For oral tilidine mono-preparations, 10 cases of "withdrawal syndrome" have been reported in the time period 1970-2012 (among 179 ADRs in total). There was only 1 case of withdrawal syndrome and one case cardiac disorder (i.e. tachycardia) in that period. During the time period 1978-2012 the VigiBase® received 505 ADRs in total for oral tilidine plus naloxone combination products, these include 18 cases of withdrawal syndrome and no case of withdrawal syndrome in combination with an ADR from the SOC "cardiac disorders".

From these data one can conclude:

- For the oxycodone mono-preparation, a statistically significant signal of disproportionate reporting was seen with regard to the occurrence of cardiac disorder events when the PRR is displayed with its 95% CI as well as with the χ^2-statistics, while for the oxycodone/naloxone FDC a statistical signal is only observed with the 95% CI.
- For the tilidine mono-preparation and the tilidine/naloxone FDC there was no signal of disproportionate reporting with respect to ADRs from the SOC "cardiac disorders"..
- The PRRs for the FDCs oxycodone/naloxone and tilidine/naloxone are numerically lower than the monopreparations and do not reveal a safety signal with regard to the risk of cardiac disorder events that might be associated with the naloxone component.
- The number of cases with withdrawal symptoms was low in all four groups and even lower for the combination of withdrawal syndrome and cardiac disorders.

EVALUATION OF DATA FROM THE BFARM SAFETY DATABASE

Introduction

In addition to the PRR assessment based on data derived from VigiBase®, data from the German Federal Institute for Drugs and Medical Devices (BfArM) safety database have been analyzed. For the oral mono-preparations of oxycodone, the oral FDC oxycodone plus naloxone and the oral FDC tilidine plus naloxone, a search for the total number of ADRs and the number of ADRs from the SOC "cardiac disorders" has been performed between the years 2006 - 2012. Note that there was no tilidine mono-preparation available on the German market during the period under investigation. Additionally, a search for the standardized MedDRA query (SMQ) "drug abuse, dependence and withdrawal" was performed. For the latter we evaluated whether patients with the ADRs "withdrawal/withdrawal syndrome" additionally have an ADR from the SOC "cardiac disorders".

Next, these data were correlated with the prescribed defined daily doses (DDD) in Germany, being derived from the respective annual prescribing reports from the German health insurances. The prescribed DDD together with the reported ADRs from the SOC "cardiac disorders", ADRs "withdrawal/withdrawal syndrome", and the combination of ADRs "withdrawal/withdrawal syndrome" with cardiac disorders for all four drug categories are presented in Tables A.6 to A.8 in Appendix 3.

Additionally, major adverse cardiovascular events (MACE) were analyzed in the BfArM database for the reporting period 2006 - 2012. The MedDRA preferred terms were queried for MACE events (myocardial infarction terms from SOC "cardiac disorders" Table A.9, Appendix 4).

Results

The reported ADRs from the SOC "cardiac disorders", ADRs "withdrawal/withdrawal syndrome", and combined reports in correlation to the DDD (estimated per 100,000 patient years) are provided in Table 10.

Table 10: Reported ADRs from the SOC "Cardiac Disorders", ADRs "Withdrawal/Withdrawal Syndrome", and ADRs "Withdrawal/Withdrawal Syndrome" in Combination with ADRs from the SOC "Cardiac Disorders" per 100,000 Patient Years in Germany, 2006-2012

	2006	2007	2008	2009	2010	2011	2012
ADRs from the SOC "cardiac disorders"							
Oxycodone Mono	20.8	14.2	8.9	4.4	6.1	6.0	11.4
Oxycodone/Naloxone	91.3	94.2	28.1	14.4	0.0	3.0	8.1
Tilidine/Naloxone	1.2	3.0	1.7	0.6	0.9	0.0	1.0
ADRs "withdrawal/withdrawal syndrome"							
Oxycodone Mono	6.9	14.2	6.7	2.2	0.0	6.0	5.7
Oxycodone/Naloxone	273.8	106.0	21.1	0.0	0.0	3.0	8.1
Tilidine/Naloxone	0.4	0.0	0.3	0.0	1.1	1.1	0.0
ADRSs "withdrawal/withdrawal syndrome" in combination with ADRs from SOC "cardiac disorders"							
Oxycodone Mono	2.3	4.7	2.2	0.0	0.0	0.0	0.0
Oxycodone/Naloxone	0.0	35.3	7.0	0.0	0.0	0.0	0.0
Tilidine/Naloxone	0.0	0.0	0.0	0.0	0.0	0.0	0.0

The FDC oxycodone/naloxone was launched in Germany in October 2006, which is why the prescribed DDDs are lower in the first years after launch as compared to the oral oxycodone mono-preparation, which has been on the German market for many years. As expected, directly after launch the number of ADRs reported for oxycodone/naloxone was higher than for the following years due to increased sensitivity of health care professionals to report ADRs of new drugs. This well known phenomenon, called Weber effect, is usually observed following market entry of a new drug product and is characterized by an increased number of reports during the first few years which thereafter start to go down [68,91,92]. In contrast, there is no signal seen for an increased frequency of ADRs from the SOC "cardiac disorders" and for "withdrawal/withdrawal syndrome" under oxycodone/naloxone treatment during the last four years. In 2009 to 2012, the cumulative reporting frequency of ADRs from the SOC "cardiac disorders" per 100,000 patient years was 5.8 for the oxycodone/naloxone FDC as compared to 7.1 for the oxycodone mono-preparation. A very low cumulative reporting frequency of cardiac ADRs was observed for the tilidine/naloxone FDC (1 cardiac disorder per 100,000 patient years in 2006-2012).

All ADRs belonging to the SOC "cardiac disorders" reported between 2006 and 2012 for oxycodone, oxycodone/naloxone and tilidine/naloxone are compiled in Table 11. In general, for several of such ADRs other suspect drugs, concomitant medication, or underlying disease might have contributed to the occurrence of the cardiac ADR as well.

Table 11: Cardiac Disorders during Oxycodone Mono (OXY), Oxycodone/ Naloxone (OXYN) and Tilidine/Naloxone (TILN) Therapy reported to the BfArM (2006-2012)

Adverse Drug Reaction	OXY	OXYN	TILN
MACE			
(Acute) myocardial infarction	2	2	1
Angina pectoris unstable	0	1	0
Arrhythmia *	1	1	0
Cardiac arrest *	0	1	0
Cardiac or cardiovascular disorder *	0	1	0
Non-MACE			
Angina pectoris	1	1	1
Atrioventricular block	1	0	0
Arrhythmia	1	1	1
(Sinus-)Bradycardia	3	1	4
(Sinus-)Tachycardia	10	2	9
Supraventricular tachycardia	0	0	1
Extrasystoles	1	0	0
Tachyarrhythmia	1	0	0
Atrial fibrillation	0	3	0
Ventricular flutter/ -fibrillation	2	0	0
Cardiac arrest	2	1	0
Cardiac insufficiency	1	2	0
Cardiac or cardiovascular disorder	2	0	3
Cardiovascular insufficiency	0	1	2
Palpitations	4	2	3
Cyanosis	1	0	0
Total	**33**	**20**	**25**

* resulting in death

Overall, the number of cardiac ADRs reported for oxycodone, oxycodone/naloxone and tilidine/naloxone between 2006 and 2012 was low considering the number of patients exposed to these drugs during this period of time. No specific, unexpected signal of a higher reporting frequency for cardiac events for the FDCs of tilidine/naloxone and oxycodone/naloxone was seen from the analysis of the BfArM safety database. When

examining cardiac events in correlation to withdrawal, it was seen that only a few reports of withdrawal syndrome occurred in combination with a cardiac disorder under oxycodone or oxycodone/naloxone treatment (for details see footnotes below Tables A.6 and A.7, Appendix 3), while no such cases were reported under tilidine/naloxone.

Concerning the ADR "withdrawal syndrome", in some cases, the respective reports also included "abuse" or the ADR "wrong dose administered". In other cases, the patient recently switched from another opioid to oxycodone/naloxone. Of note, from 2009 to 2012 the reporting frequency of withdrawal in combination with a cardiac event was 0.0 in 100,000 patient years for oxycodone, the oxycodone/naloxone FDC, and the tilidine/ naloxone combination.

Overall, the analysis of MACE events in the BfArM database does not demonstrate or support the identification of a safety signal for the FDCs of oxycodone/naloxone or tilidine/naloxone.

4.3.4 Clinical Trial Safety Data and Postmarketing Data for Targin® from the Mundipharma Drug Safety Department

Develco received additional postmarketing data and safety data from clinical trials for the FDC product containing oxycodone and naloxone (Targin®/Targinact®) from Mundipharma.

Clinical trial data

The data from randomized double-blind clinical trials involving approximately 4,000 patients treated with oxycodone PR/naloxone PR were analyzed and medically reviewed to specifically investigate whether there might be any indication of an increase of cardiovascular events or unspecified cases of death towards reference treatment. This involved a review of 236 cases with 397 serious adverse events (SAEs) from double-blind clinical trials received up to 15 December 2012. The complete cardiac and nervous SOC has therefore been scrutinized for any MedDRA preferred terms (PTs) of potential interest. Out of the total number of 236 cases, 19 cases with 20 SAEs of the following kind of cardiovascular events were observed:

• Acute myocardial infarction	• Cardio-respiratory arrest	• Myocardial infarction
• Angina pectoris	• Cerebrovascular accident	• Myocardial ischemia
• Angina unstable	• Death (unspecified)	• Transient ischemic attack.
• Cardiac arrest	• Ischemic stroke	

Upon review, the unique 20 SAEs in these 19 cases were all rated as either unlikely or not related to the study medication by the investigators except for one case in the active

comparator group which had been coded as possibly related. The cases from these randomized double-blind-clinical trials could be allocated to the treatment arms as follows:

- **Oxycodone/Naloxone:** 4 cases (angina unstable n = 1; cardio-respiratory arrest n = 1; death n = 2). The 2 unspecified fatal cases occurred in cancer patients. Fatality was assessed as due to the underlying disease.

- **Blinded:** 4 cases (acute myocardial infarction n = 1; angina pectoris n = 2; myocardial infarction n = 1). One of the cases was on oxycodone/naloxone during the run-in phase, but on blinded study medication when the SAE occurred.

- **Oxycodone:** 7 cases (cardiac arrest n = 1; cerebrovascular accident n = 3; ischemic stroke n = 1; myocardial infarction n = 2; myocardial ischemia n = 1). One case had 2 SAEs (myocardial infarction and myocardial ischemia).

- **Codeine/Paracetamol:** 2 cases (angina pectoris n = 2)

- **Placebo:** 2 cases (acute myocardial infarction n = 1; transient ischemic attack n = 1).

In none of the 19 cases was an adverse event of drug withdrawal syndrome reported.

Four of the overall 15 unblinded patients involved subjects on oxycodone/naloxone therapy (with four additional cases still blinded). The randomization to treatment in the double-blind phases was performed in balanced manner for active comparator (almost exclusively 1:1), thus leading to a proportional patient exposure across these two treatment arms (oxycodone/naloxone with n = 4 SAEs and active comparator with n = 9 SAEs). Patient exposure to placebo was much lower; accordingly the occurrence of 4 SAEs under oxycodone/naloxone is relatively less compared to 2 SAE cases under placebo.

There is no indication of an excess risk of the cardiovascular events in question in subjects treated with oxycodone/naloxone as study medication opposed to subjects being treated with active or non-active comparator. Likewise, from the randomized double-blind clinical trial data there is no indication supporting the hypothesis that the naloxone component as part of the fixed combination product might induce cardiovascular events subsequent to the occurrence of a drug withdrawal syndrome.

Postmarketing data

A cumulative search of the international drug safety database was performed as of 08 September 2013 for cases (not included in the double-blind clinical trial data set) with a suspect drug from the oxycodone/naloxone drug family which reported one or more MedDRA PTs indicative of drug withdrawal and then one or more MedDRA PT from the SOCs “cardiac disorders”, “vascular disorders”, or “nervous system disorders”.

Of the 255 cases identified reporting drug withdrawal syndrome, 19 cases contained 19 adverse events falling under the SOCs “cardiac disorders”, “vascular disorders”, or “nervous

system disorders". None of the cardiac events entailed myocardial infarction. Four of the 19 adverse events referred to tachycardia (one serious), three to palpitations (non-serious) and two to increased blood pressure (one serious). The remainder of cases referred to different event types. There were no events of interest under the SOC "nervous system disorders" (such as stroke or transient ischemic attack), and likewise there were no occurrences of unspecified death.

SUMMARY AND CONCLUSION OF POST-MARKETING DATA WITH ORAL NALOXONE PRODUCTS

From the prescription data, the data from the VigiBase®, the BfArM safety database, and Mundipharma's drug safety reporting, one can deduce that:

- Millions of patients have been exposed to the FDCs of tilidine/naloxone and oxycodone/naloxone which are widely used for long-term treatment of mild-to-moderate and moderate-to-severe pain.
- PRR analysis from the WHO Collaborating Centre does not demonstrate or support the identification of a cardiac safety signal for the oxycodone/naloxone and tilidine/naloxone FDCs that might be associated with the naloxone component.
- No specific, unexpected signal of a higher reporting frequency for cardiac events for the FDCs of tilidine/naloxone and oxycodone/naloxone was seen from the analysis of the BfArM safety database. For both FDCs, no safety signal was observed for MACE.
- Only a small number of cases of "withdrawal/withdrawal syndrome" were obtained from the WHO Collaborating Centre and the BfArM safety database. Even fewer cases reporting both withdrawal and cardiac disorder events were observed. There was no signal for cardiac disorders in patients with withdrawal under treatment with tilidine/ naloxone or oxycodone/naloxone.
- Safety data from double-blind clinical trials and postmarketing data from the international safety database for the oxycodone/naloxone FDC (Targin®/Targinact®) provided by Mundipharma support the absence of a higher risk for cardiovascular events related to naloxone and the lacking indication for an association between drug withdrawal and cardiovascular events.

In conclusion, a relationship between oral naloxone and the occurrence of cardiovascular disorders cannot be drawn from the analyses of these post-marketing safety databases and the data provided by Mundipharma for Targin®/Targinact®.

4.4 Summary and Conclusion on Cardiovascular and Long-term Safety of Oral Naloxone HCl PR Tablets

Develco has critically reviewed available data about whether orally administered naloxone in the treatment of OIC may pose serious cardiovascular safety concerns. In the above sections, the company has provided considerations reflecting the oral bioavailability of naloxone, naloxone's receptor binding and related signal transduction as well as prescription data of oral naloxone FDC products and corresponding cardiac safety signals in pharmacovigilance databases.

Due to the fact that oral naloxone in the treatment of OIC acts locally at μ-opioid receptors in the gut, it can be regarded as a locally applied, locally acting drug. Naloxone is almost completely eliminated via pre-systemic metabolism (oral bioavailability of less than 2%), forming predominantly naloxone-3-glucuronide. Naloxone-3-glucuronide shows negligible opioid receptor affinity and is therefore considered devoid of any peripheral or central antagonistic activity.

Develco also assessed post-marketing pharmacovigilance data to analyze cardiovascular safety signals attributable to oral naloxone. Naloxone is well established in Europe in oral products combined with opioids to counteract OIC or to deter opioid misuse. Oral naloxone products have been administered to millions of patients in Germany alone, and the pattern of use indicates that patients who chronically use these products are typically on higher doses of naloxone than patients on short-term treatment. Analysis of the safety databases from WHO and the German health regulatory authority indicate that there is no evidence of a cardiovascular safety signal

Published reports and Develco's own clinical pharmacokinetics studies indicate that naloxone does not achieve appreciable systemic exposure, and that the vast majority of the compound is converted to the inactive metabolite naloxone-3-glucuronide. The low systemic availability of the parent molecule suggests that oral prolonged-release naloxone is highly unlikely to cause adverse systemic effects, including adverse cardiovascular effects. The prescription data described in section 4.3 provide information about real-life usage of oral prolonged-release naloxone in a large patient population. In pharmacovigilance databases there was no evidence of increased cardiovascular risk or a clear association of cardiovascular events with withdrawal. Therefore, the post-marketing results support the lack of a cardiovascular risk anticipated from the clinical pharmacokinetic properties. In aggregate, available data do not suggest or support the identification of a cardiovascular safety signal for oral prolonged release naloxone and, as such, a pre-approval cardiovascular safety outcome trial would not be required.

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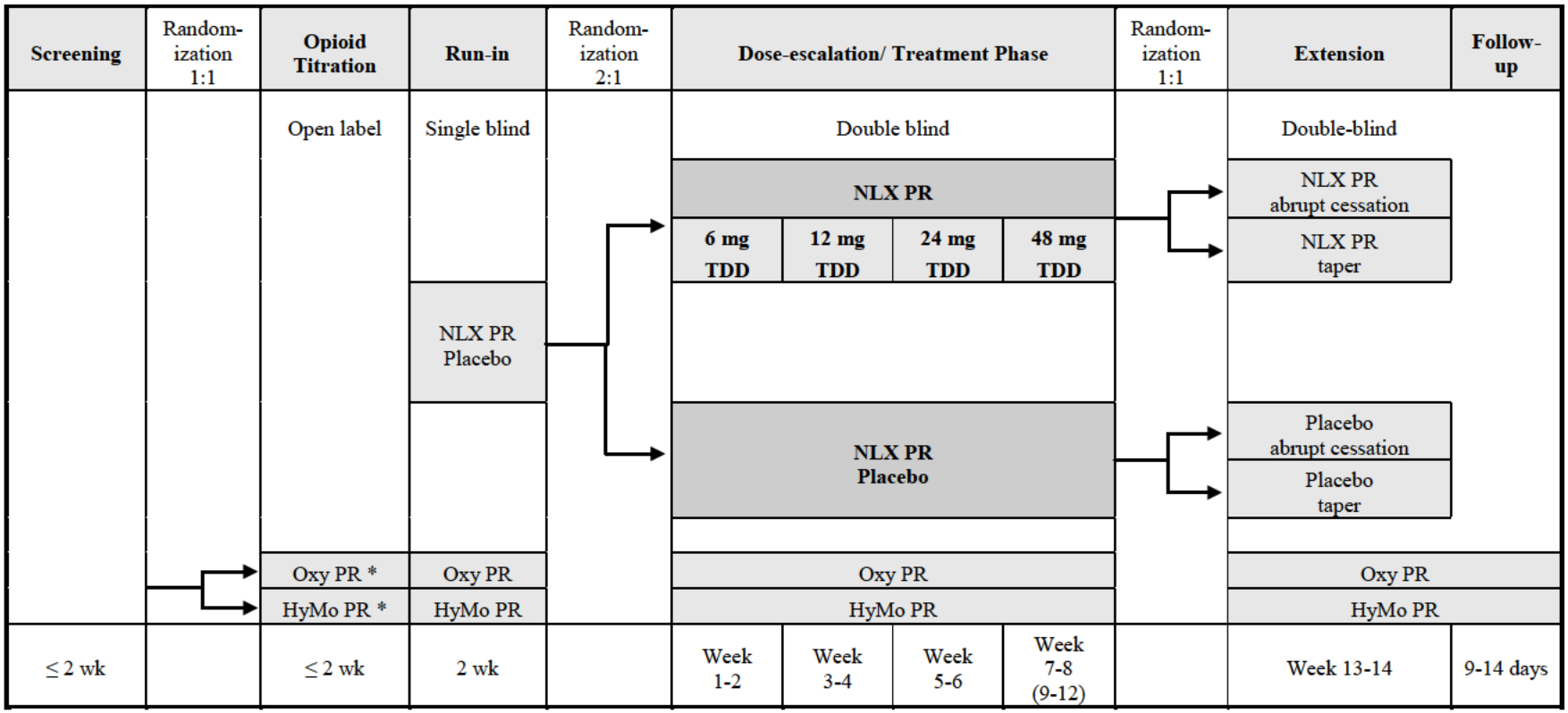
Appendix 1 Flow Chart of Study 0176/DEV



Patients who de-escalate during the treatment phase will continue at the de-escalated dose for the remainder of the treatment phase

Dosing is BID in Study 0176/DEV and QD in Study 0177/DEV, but total daily dose of naloxone is the same for both studies

* The total daily dose (TDD) of oxycodone and hydromorphone determined for each patient at the end of the opioid titration phase will be maintained throughout the entire study

Oxy: oxycodone; HyMo: hydromorphone; NLX: naloxone; PR: Prolonged Release; TDD: Total Daily Dose

Appendix 2 Additional data concerning the Evaluation of data from the WHO Collaborating Centre for International Drug Monitoring

Table A.1: Number of ADRs from SOC "Cardiac Disorders", All Other SOCs, and Total Number of ADRs Reported for Oxycodone, Oxycodone/Naloxone, Tilidine, and Tilidine/Naloxone in Comparison to All Other Medicinal Products

VigiBase®

	SOC "cardiac disorders"	All other SOCs	Total number of ADRs
Oxycodone *	1,757	9,109	10,866
All other medicinal products *	414,531	5,689,980	6,104,511
Oxycodone/Naloxone **	43	410	453
All other medicinal products **	290,430	4,138,537	4,428,967
Tilidine ***	13	166	179
All other medicinal products ***	502,664	7,328,739	7,831,403
Tilidine/Naloxone ******	30	475	505
All other medicinal products ******	497,684	7,230,730	7,728,414

* data from 1998-2012
** data from 2006-2012
*** data from 1970-2012
**** data from 1978-2012

Please note that in the following tables (i.e. Tables A.2 - A.4) the total number of ADRs (i.e. events) is given, whereas for the computation of the PRR the number of cases with at least one ADR from the SOC "cardiac disorders" were counted (see Table 6).

Table A.2: List of ADRs from the SOC "Cardiac Disorder" for Oral Oxycodone Mono-preparations in the Time Period 1998 - 2012 from the WHO Database

Cardiac disorders	Total 2,023
Acute coronary syndrome	1
Acute myocardial infarction	7
Agonal rhythm	1
Angina pectoris	10
Angina unstable	5
Aortic valve calcification	1
Aortic valve incompetence	3
Aortic valve sclerosis	1

Cardiac disorders	**Total 2,023**
Aortic valve stenosis	1
Arrhythmia	27
Arteriosclerosis coronary artery	20
Atrial fibrillation	24
Atrioventricular block	2
Atrioventricular block first degree	7
Atrioventricular dissociation	1
Bradyarrhythmia	1
Bradycardia	33
Bundle branch block	3
Bundle branch block left	1
Bundle branch block right	8
Cardiac arrest	692
Cardiac disorder	44
Cardiac failure	15
Cardiac failure acute	1
Cardiac failure congestive	34
Cardiac fibrillation	2
Cardiac flutter	2
Cardiac hypertrophy	3
Cardiac valve disease	2
Cardiac valve sclerosis	1
Cardiomegaly	52
Cardiomyopathy	8
Cardiopulmonary failure	3
Cardio-respiratory arrest	409
Cardiotoxicity	1
Cardiovascular disorder	10
Conduction disorder	1
Congestive cardiomyopathy	3
Cor pulmonale	1
Coronary artery disease	16
Coronary artery occlusion	6
Coronary artery stenosis	5
Coronary artery thrombosis	1
Cyanosis	50
Dilatation atrial	4
Dilatation ventricular	2
Extrasystoles	3
Hypertensive heart disease	10
Hypertrophic cardiomyopathy	3

Cardiac disorders	**Total 2,023**
Left ventricular dysfunction	1
Left ventricular failure	1
Left ventricular hypertrophy	3
Mitral valve calcification	3
Mitral valve incompetence	6
Mitral valve prolapse	3
Myocardial fibrosis	6
Myocardial infarction	92
Myocardial ischemia	6
Myocarditis	1
Nodal arrhythmia	1
Nodal rhythm	4
Palpitations	66
Pericardial disease	1
Pericardial effusion	6
Pericardial hemorrhage	1
Pericarditis	5
Pericarditis adhesive	1
Pulseless electrical activity	1
Right ventricular dysfunction	1
Sick sinus syndrome	1
Sinus arrhythmia	5
Sinus bradycardia	5
Sinus tachycardia	88
Stress cardiomyopathy	1
Supraventricular extrasystoles	2
Supraventricular tachycardia	6
Tachyarrhythmia	2
Tachycardia	116
Torsade de pointes	2
Tricuspid valve incompetence	3
Ventricle rupture	1
Ventricular arrhythmia	4
Ventricular dysfunction	2
Ventricular extrasystoles	16
Ventricular fibrillation	7
Ventricular flutter	1
Ventricular hypertrophy	5
Ventricular hypokinesia	3
Ventricular tachycardia	3

Table A.3: List of ADRs from the SOC "cardiac disorder" for the FDC Oxycodone/Naloxone in the Time Period 2006 - 2012 from the WHO Database

Cardiac disorders	Total 48
Acute myocardial infarction	2
Angina pectoris	5
Angina unstable	1
Arrhythmia	3
Atrial fibrillation	6
Bradycardia	1
Bundle branch block right	2
Cardiac arrest	1
Cardiac disorder	1
Cardiac failure	4
Cardiovascular disorder	1
Cardiovascular insufficiency	1
Cyanosis	1
Extrasystoles	1
Myocardial infarction	4
Palpitations	5
Right ventricular failure	1
Sinus bradycardia	1
Supraventricular extrasystoles	1
Tachycardia	6

Table A.4: List of ADRs from the SOC "Cardiac Disorder" for Oral Tilidine Mono-preparations in the Time Period 1970-2012 from the WHO Database

Cardiac disorders	Total 15
Arrhythmia	2
Bradycardia	4
Cardiac arrest	1
Cyanosis	1
Left ventricular failure	1
Tachycardia	6

Table A.5: List of ADRs from the SOC "Cardiac Disorder" for the FDC Tilidine/Naloxone in the Time Period 1978 – 2012 from the WHO Database

Cardiac disorders	**Total 32**
Angina pectoris	1
Arrhythmia	1
Bradycardia	8
Cardiac discomfort	2
Cardiovascular disorder	1
Cardiovascular insufficiency	2
Myocardial infarction	1
Palpitations	5
Supraventricular tachycardia	1
Tachycardia	10

Appendix 3 Additional data concerning the Evaluation of data from the BfArM safety database

Table A.6: Oxycodone Mono - Prescribed Defined Daily Doses and Reported ADRs in Germany, 2006-2012

	2006	2007	2008	2009	2010	2011	2012	Total/ Cumulative
DDD (75 mg) in millions*	15.8	15.4	16.4	16.5	17.9	18.2	19.2	119.4
Total No. of ADRs	163	94	104	84	67	68	113	691
ADRs from the SOC cardiac disorders	9	6	4	2	3	3	6	33
ADR withdrawal/ withdrawal syndrome	3	6	3	1	0	3	3	19
ADRs withdrawal/ withdrawal syndrome plus ADRs from the SOC cardiac disorder**	1	2	1	0	0	0	0	4

*According to Schwabe and Paffrath, 2007-2013 [57].

** ADRs from SOC cardiac disorders: palpitations (2006), arrhythmia, tachycardia (2007), cardiac arrest (2008)

Table A.7: Oxycodone/Naloxone - Prescribed Defined Daily Doses and Reported ADRs in Germany, 2006-2012

	2006	2007	2008	2009	2010	2011	2012	Total/ Cumulative
DDD (75 mg) in millions*	0.4	3.1	5.2	7.6	10.7	12.2	13.6	52.8
Total No. of ADRs	48	156	130	63	108	74	88	667
ADRs from the SOC cardiac disorders	1	8	4	3	0	1	3	20
ADR withdrawal/ withdrawal syndrome	3	9	3	0	0	1	3	19
ADRs withdrawal/ withdrawal syndrome plus ADRs from the SOC cardiac disorder**	0	3	1	0	0	0	0	4

*According to Schwabe and Paffrath, 2007-2013 [57].

** ADRs from the SOC cardiac disorders: arrhythmia, tachycardia, cardiac arrest (2007), palpitations (2008)

Table A.8: Tilidine/Naloxone - Prescribed Defined Daily Doses and Reported ADRs in Germany, 2006-2012

	2006	2007	2008	2009	2010	2011	2012	Total/ Cumulative
DDD (0.2 g) in millions	89.2	96.7	107.6	120.2	127.8	136.2	143.1	820.8
Total No. of ADRs	112	135	118	81	130	64	106	746
ADRs from the SOC cardiac disorders	3	8	5	2	3	0	4	25
ADR withdrawal/ withdrawal syndrome	1	0	1	0	4	4	0	10
ADRs withdrawal/ withdrawal syndrome plus ADRs from the SOC cardiac disorder	0	0	0	0	0	0	0	0

* According to Schwabe and Paffrath, 2007-2013 [57]. Of note there was no Tilidine monopreparation available for comparison.

Appendix 4 Terms Considered as MACE

Table A.9: List of Terms from the SOC "Cardiac Disorders" Considered as MACE

Acute myocardial infarction	Postprocedural myocardial infarction
Coronary artery thrombosis	Silent myocardial infarction
Myocardial infarction	Instable angina pectoris
Papillary muscle infarction	Death in combination with an ADR from the SOC "cardiac disorder"